ASSESSING CLINICAL PRACTICES AND BELIEFS AMONG PROVIDERS FOLLOWING WOMEN DIAGNOSED OR AT-RISK FOR FABRY DISEASE

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BS, University of Washington, 2013

Submitted to the Graduate Faculty of

the Department of Human Genetics

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science and Master of Public Health

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

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ABSTRACT

For women with Fabry disease, there are several factors which can influence the level of a patient's engagement with the healthcare system to manage her disease. Unfortunately, some of these factors have the potential to reduce the likelihood that a female patient will become an active participant in her own medical management because of the influence on the patient's perception of her own disease susceptibility and personal health beliefs, thus increasing her risk for negative Fabry-disease related health outcomes. These factors, such as the past history of labeling women as asymptomatic carriers and the influence of disease burden on the mental health of the patient, are structural and psychosocial in nature, and collectively contribute to the barriers perceived by women to engaging in disease management. Recognizing the multi-faceted origins and complexity of these factors, our team developed a three part project to examine contributing factors and their origins to these barriers. Parts one and two of this project focused on characterizing the health beliefs of females with Fabry disease using the Health Belief Model and identified patients' perceived severity, susceptibility, and benefits to engaging in Fabry disease related care. This study, part three of the project, focuses on a different source, aiming to characterize Fabry healthcare providers' clinical practices and beliefs in order to assess their potential role in the contributions to these barriers. By surveying 58 healthcare providers from a variety of locations, potential areas of clinical practice that may influence the health beliefs and barriers of women with Fabry disease were identified, including discrepancies in clinical practice

across providers of differing levels of experience, the inconsistent adherence to clinical practice guidelines, and use of the term “carrier” by providers to describe female patients. Understanding the presence of these factors allows for strategies to be developed that can address these barriers, and in turn, optimize clinical health outcomes for female Fabry patients. Furthermore, these strategies can be applied to address barriers for women affected by other X linked conditions, thus signifying the potential for a public health intervention based on the results of this three part project.

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PREFACE

I have learned so much from this project, which would not have been possible without the time, commitment, and support from the members of my thesis committee. For this, I am truly grateful to Nadene Henderson, Robin Grubs, Todd Bear, and David Finegold for their contribution to my growth and learning throughout this process. I would like to specifically thank Nadene Henderson and David Finegold for granting me the amazing opportunity to immerse myself in the world of lysosomal storage disorders at the LSD clinic at the Children's Hospital of Pittsburgh. My deepest gratitude goes to Todd Bear for his patience and inclination to assist me with several steps of this project during multiple long and tedious sessions. I would also like to specially thank you to Robin Grubs for her continuous support and guidance throughout these last two years. You were there for me at every step of the way, and for that I am ever grateful.

It is also important that I acknowledge the endless support and care I received from my family, friends, and classmates. Without this phenomenal group of women, I would not have had the strength to emerge from this process successfully. Thank you for being there to listen, and to provide your encouragement.

Lastly, to my fiancé Walter, your strength, love, and support held me up over these years as you constantly stayed by my side. Whenever I felt that I did not have what it takes to achieve my goals, you always gave me the encouragement I needed to reach them. Your everyday love, compassion, and friendship are what enabled me to succeed.

1.0 INTRODUCTION

Fabry disease is a rare X-linked lysosomal storage disorder that results in the accumulation of glycosphingolipids throughout the vasculature endothelial cells of the body due to a deficiency of an enzyme called α-galactosidase A.[1] Over time, progressive accumulation of glycosphingolipid substrates leads to a number of chronic symptomatic manifestations, some of which can be life threatening, involving several organ systems.[2,3] Both males and females who harbor a pathogenic mutation in the galactosidase alpha (*GLA*) gene are at-risk for developing symptoms, however, the spectrum of clinical manifestations is known to be wider among heterozygous females.[4] Previously, health professionals assumed that females could not be affected by the disease due to the fact that females possess a working copy of the gene, however more recent evidence indicates that asymptomatic female heterozygotes are the exception and not the rule.[5]

With differences in the course of disease experienced by the population of Fabry affected females, new challenges for the healthcare providers caring for these individuals arise. Heterozygous females not only require a different method of diagnosis from their male counterparts, but the clinical care guidelines for initiation of therapies must be adapted to the needs of female heterozygotes as well. Female heterozygotes are at risk for significant manifestations of Fabry-related symptoms and therefore necessitate appropriate monitoring and treatment.[5] At present, generalized practice guidelines for care of patients with Fabry disease

state that disease monitoring for both men and women take place with a team of multi-disciplinary specialists on an annual or semi-annual schedule. These guidelines however differ between men and women regarding initiation of primary therapy, stating that initiation should take place by the age of 10 to 13 in males regardless of disease burden and only when significant clinical manifestations take place for females.[6] However, multiple research studies evaluating the effectiveness of primary Fabry therapy in both men and women have concluded that initiation of therapy should take place before the first signs of disease are present, and therefore, are in conflict with current practice guidelines.[7–10] In addition to inconsistencies in practice guidelines, other challenges heterozygous females face such as the uncommonness of Fabry disease, the prevailing misconception that female heterozygotes are unaffected carriers of the disease or only express mild symptoms, and the disparity between healthcare treatment of men and women in the context of limited objective evidence further compound to raise barriers to adequate disease management, monitoring, and treatment. Together, these challenges, some of which are unique to female heterozygotes, have the unusual potential to allow for miscommunication between the patient and the provider that can hinder optimal disease management, monitoring, and treatment.[11]

The Lysosomal Storage Disorders (LSD) Program at the University of Pittsburgh and the Children's Hospital of Pittsburgh of UPMC is dedicated to addressing the healthcare needs of patients who are affected by a lysosomal storage disorder, including Fabry disease, and their families. This longstanding program has seen several dedicated providers come and go, as well as a few providers who have remained through the years, but the devotion to the patients remains unfaltering. A research project that aimed to characterize the unique clinical experiences and health beliefs of females diagnosed or at-risk for Fabry disease and their influencing factors was

originally conceived by two individuals of the LSD team, Dr. David Finegold, MD and genetic counselor Katie Long, MS, CGC. In their observations of their own female patients with Fabry disease, they noted that many of their heterozygous female patients were inconsistently clinically evaluated unless they presented with severe manifestations of the disease. Even more so, this trend appeared to take place despite recommendations for regular evaluation by healthcare professionals, an observation which was consistent with what had been reported in the current medical literature. A handful of studies had noted that heterozygous females frequently dismissed their own risk to develop significant Fabry-related manifestations and were more likely to attend genetic counseling and clinical evaluation appointments as an accompaniment of an affected male relative rather than for their own health management.[2,5] Still, while the difference between males and females regarding their engagement in clinical monitoring had been identified, the psychosocial mechanisms driving this phenomenon had yet to be understood. Therefore, in order to capture and characterize the unique clinical experiences and health beliefs of females diagnosed or at-risk for Fabry disease, and their influencing factors, Ms. Long and Dr. Finegold designed a three part study to investigate multiple facets of the issue.

Part one of this project focused primarily on achieving an understanding of the health beliefs of females who were diagnosed or at risk for Fabry disease. This was accomplished by conducting interviews with ten adult females affiliated with the LSD program who had a confirmed diagnosis of Fabry disease or a diagnosis based on family history. Utilizing the Health Belief Model as the structure to focus the content of the interview questions and thematic analysis to analyze the interview transcripts, the investigators were able to gain a more in-depth understanding of the personal beliefs of the participants. Part one revealed that the participants generally believed that Fabry disease was a serious disease but some individuals expressed

uncertainty with regard to severity and timing of symptom onset of the disease among females, especially when compared to the severity and timing of onset among males. Participants also demonstrated an understanding of the natural history of Fabry disease but in general lacked a perception of personal susceptibility to manifestations. Some participants even went on to acknowledge their own feelings of denial or inability to emotionally handle the implications of being a symptomatic mother, sister, daughter, or caretaker for a male relative, however others expressed inevitability to developing manifestations of Fabry disease, feeling susceptible despite following recommended monitoring and treatment. Several themes related to barriers were identified in participants' responses including denial, grief, guilt, excessive worry, and sadness that influenced decision making with regards to engaging in routine evaluations, monitoring, and treatment. Additionally, themes of duty and loyalty as well as modeling the caretaker role among women with a symptomatic male relative were noted.

Part two of this project used the themes identified in part one to design a questionnaire to gain further insight into the health beliefs among a broader group of women diagnosed or at-risk for Fabry disease. For this part, the specific interest was focused in assessing barriers to engaging in preventative health behaviors in order to develop strategies to address these barriers and improve patient compliance with recommended therapies. Forty-four women participated in the study and the findings of part two were consistent with the findings of part one in that participants adequately understood the severity of Fabry disease for both males and females, but they viewed their personal susceptibility in a different manner. Additionally, participants' perception of the appropriateness for the term "carrier" did not necessarily reflect their own perception of their ability to develop symptoms, but it was noted by the investigators that the use of this term could allow for possible miscommunications between participants and their

providers. Other findings included participants' expectations of treatment with enzyme replacement therapy (ERT) which were not completely consistent with known clinical benefits of the therapy. Furthermore, new causes of perceived barriers to treatment and evaluation were identified in this study and included the financial burden of primary therapy as well as distance from treatment centers, anxiety, and feelings of being overwhelmed. However, a statistically significant difference between evaluations recommended to and completed by participants was not identified during the analysis of this study when investigating potential modifying variables and cues to action.

This current study exists as part three in the project. It differs from the first two parts of the study in that assessment is focused on the practices and opinions of healthcare providers who are involved in the care of women who are either diagnosed or at-risk for Fabry disease. A questionnaire was designed by using elements of concern that were identified in previous parts of the project, this time to quantitatively capture provider views of importance regarding different facets of Fabry-related care and adherence to published practice guidelines for Fabry disease. Additionally, the survey was also designed to collect data on the terms used by providers when describing asymptomatic and symptomatic female patients. The population recruited for this study contained a variety of participant backgrounds within the field of genetics, allowing for comparison of response behavior between differing groups of participants, thus providing insight to the spectrum of practices among healthcare providers.

Collectively, the three parts of this project provide insights to the health beliefs of the female Fabry population with a specific interest in assessing barriers to engaging in preventative health behaviors, the clinical practices of providers caring for these individuals, and how the perceptions of these two groups align. With careful analysis, this project may help to contribute

to the development of strategies to address these barriers, improve patient compliance with recommended therapies, and optimize clinical outcomes.

1.1 SPECIFIC AIMS

The specific aims of this project are as follows: (1) To design and administer a questionnaire for providers, distributed to various medical institutions within the United States through an anonymous online survey. (2) To collect data via the questionnaire on the practices and beliefs of medical providers regarding the importance of clinical evaluation, continued monitoring, and treatment for females who are diagnosed or at-risk for Fabry disease as well as disease knowledge and symptoms, inheritance pattern, and recurrence risk of women with Fabry disease. (3) To collect data via the questionnaire on provider adherence to published recommendations for the management of females who are diagnosed or at-risk for Fabry disease. (4) To collect data via the questionnaire on healthcare provider views on the current usage and perceived appropriateness of the term “carrier” to describe females who are diagnosed or at-risk for Fabry disease. (5) To collect data via the questionnaire in order to assess the differences, if any, in the different categories of providers regarding the risk beliefs and care of females diagnosed or at-risk for Fabry disease (i.e. primary care, cardiology, nephrology, gastroenterology, etc.).

2.0 LITERATURE REVIEW

2.1.1 Fabry Disease

Fabry disease, also known as Anderson-Fabry disease, is a rare heritable lysosomal storage disorder that causes a gradual accumulation of a glycosphingolipid substrate, globotriaosylceramide (GL-3), in the lysosomes of cells due to insufficient levels or functioning of the α-galactosidase A enzyme.[1] The accumulation of GL-3 throughout the body can cause a wide-range of clinical symptoms as severe as cerebrovascular disease, cardiac arrest, and end-stage renal disease.[2,3] Fabry disease is inherited in an X-linked pattern and affects both men and women of all ethnicities with an estimated prevalence of 1 in 40,000 to 1 in 117,000 based on clinical ascertainment.[12] However, being an under-recognized condition, Fabry disease is often misdiagnosed due to its rarity and variable presentation of features, commonly leading to inappropriate or complete lack of treatment for affected patients.[12] Newborn screening efforts in several countries have revealed that the estimated prevalence rate of Fabry disease is higher than originally estimated, with studies estimating a prevalence range of 1 in 1,250 to 1 in 7,057.[13–17] Additionally, studies conducting Fabry screening in high risk populations such as patients with hypertrophic cardiomyopathy have identified a higher prevalence than originally presumed.[18]

2.1.1.1 Molecular Genetics and Pathogenesis

The underlying cause of Fabry disease is a disruption to the α-galactosidase A enzyme which is encoded by the *GLA* gene, located at position Xq22.1. The α-galactosidase A enzyme is responsible for catalyzing the hydrolytic cleavage of the terminal molecule of galactose from the substrate globotriaosylceramide (GL3).[1,19] Without this cleavage, neutral glycosphingolipids accumulate throughout various organ systems over time in the lysosomes of cells leading to damage of the glomerular and tubular epithelial cells, the myocardial cells and valvular fibrocytes, neurons of the dorsal root ganglia and autonomic nervous system, as well as the endothelial, perithelial, and smooth muscle cells of the vascular system, eventually progressing to the various clinical symptoms that are characteristic of Fabry disease.[20,21] The *GLA* gene is the only known gene to cause Fabry disease. To date, over 800 different pathogenic variants have been identified across a broad range of ethnic groups consisting of a wide variety of mutation types, including point mutations, splicing defects, and genomic rearrangements.[22] This result, along with the fact that many affected families have their own unique mutation, make genotype to phenotype correlations difficult to predict.[22,23]

2.1.1.2 Clinical Course of Fabry Disease

Fabry disease is a multi-systemic condition resulting from the build-up of lysosomal GL3 throughout the body. Symptoms arising from the disease are chronic and progressive in nature and although variable, can include manifestations in multiple organ systems including the renal, cardiac, neurologic, cerebrovascular, ophthalmologic, gastrointestinal, and dermatologic systems.[2,3,12,24] Individuals diagnosed with Fabry disease may experience any combination of these symptoms due to both the disease presentation and severity being highly variable even between blood-related individuals.[20,24,25] Of note, the highest levels of morbidity and mortality in

Fabry disease are attributed to renal insufficiency, central and peripheral disease of the nervous system, and cardiovascular disease.[2,3,25]

In the past, women were thought to not at-risk for development of Fabry disease symptoms however, it is now recognized that heterozygous women can experience clinical symptoms similar to their affected male counter parts, although with greater variability in clinical presentation. Approximately 60-70% of females heterozygous for the condition are estimated to experience at least one form of Fabry symptom.[4] Overall, males and females differ in their Fabry disease presentations in that females as a group experience a wider spectrum of disease severity.[12,24] For both men and women, first symptoms typically occur in childhood with the average age of disease onset occurring between 6 to 8 years in males and around 9 years for females.[26,27]

The earliest and most common clinical manifestations to present in an affected individual's lifetime are typically neurological, gastrointestinal, and ophthalmologic symptoms.[26,27] Neurological symptoms contribute the largest aspect of the disease burden experienced in the pediatric population and include acroparaesthesia (sensations of burning and tingling) of the hands and feet, pain crisis, generalized pain, altered temperature sensitivity, and dyshidrosis. Gastrointestinal symptoms include abdominal cramping, constipation, and diarrhea that can be severe enough to cause school absences. Ophthalmologic symptoms have not been reported as burdensome to the quality of life of pediatric patients however manifestations including cornea verticillata and tortuous vessels in the absence of hypertension can present in individuals even before the age of five.[26,28]

Other clinical manifestations that may present over the lifetimes of individuals with Fabry disease are collectively not as common as the symptoms mentioned previously but are

significant. These multi-systemic symptoms include angiokeratoma, tinnitus, hearing loss, vertigo, obstructive pulmonary disease, and various psychological conditions including panic attacks, depression, and adaptive functioning disorders.[2,3,21,29–31]

The most clinically significant symptoms with the highest contribution to mortality in Fabry disease when left untreated are renal, cardiac, and cerebrovascular manifestations.[25,28,32] End-stage renal failure, requiring chronic dialysis or renal transplantation, occurs in approximately 31% of males and 1-4% of females but more common renal involvement includes symptoms such as proteinuria, hypertension, and chronic renal insufficiency. Typically, such symptoms present in the second to third decades of life, however manifestations have been reported in individuals less than 10 years old.[26,27] Untreated cardiac disease symptoms can progress to congestive heart failure or episodes of myocardial infarctions. Symptoms include conduction, rhythm, and valvular abnormalities, cardiomyopathy, and left ventricular hypertrophy.[2,3] Additionally, cerebrovascular manifestations as severe as transient ischemic attacks and strokes present in affected individuals with an average age of onset of 34 years old for men and 40 years old for women.[28]

The disease burden and severity of the various clinical manifestations of Fabry disease results in a shortened lifespan of individuals affected with the disease. For affected men, the median life expectancy is 58.2 years, compared to 74.8 years in the healthy general U.S. population. For affected women, the median life expectancy is 75.4 years, compared to 80.1 years in the healthy general U.S. population. This difference seen between men and women likely reflects the variable presentation and delayed age of onset recognized in the clinical course of affected women as compared to men.[32] Enzyme replacement therapy treatment is likely to improve the lifespan outcomes for individuals with Fabry disease, however as of this point in

time, life expectancy for males and females has not been evaluated in the context of enzyme replacement therapy status.[33]

2.1.1.3 Inheritance Pattern and Recurrence Risk

The *GLA* gene responsible for Fabry disease is localized to the X chromosome at position Xq22.1, causing the disease to be inherited in an X-linked pattern.[33] Women who are heterozygous for the mutation have a 50% chance of passing on the mutant allele with every pregnancy while hemizygous males will always pass on the mutant allele to their daughters but never to their sons, as one of the features of X-linked inheritance is that there is never male-to-male transmission. *De novo* mutations in the *GLA* gene are quite rare.

Previously, it was believed that only men could be affected with symptoms of Fabry disease while women were labeled as asymptomatic carriers.[25] However, more recently it has been discovered that many heterozygous women experience clinical symptoms similar to those of men with Fabry disease in higher proportions than have been previously recognized.[12,24,34–36] Furthermore, there is a great degree of clinical variability among heterozygous females which is not well understood. One suggested mechanism is that skewed X-inactivation could provide an underlying mechanism for such variability where more severely affected women are likely to express the X chromosome with the *GLA* mutation in affected organs.[24] However, evidence from several studies do not support this claim.[5,37,38] Another likely explanation is the influence of undiscovered genetic and environmental factors on the expression of Fabry symptoms.[39] Nevertheless, there is no longer any question to the potential for at-risk women to develop any or all symptoms of Fabry disease including premature death. Because of this knowledge, the current recommendation is to refer to women with a *GLA* mutation as a "heterozygote" instead of a

"carrier" in order to avoid conveying the incorrect assumption that women are not at-risk to develop Fabry disease related symptoms.[24,40]

2.1.1.4 Diagnosis

For many reasons a clinical diagnosis of Fabry disease is difficult to make. The primary symptoms of Fabry disease are not specific and can be confused with other diseases, there is a wide variability of clinical presentations among patients, and the disease involves multiple organ systems. Often, the unclear presentation of the symptoms of Fabry disease, in conjunction with its rarity, result in a prolonged delay of an accurate diagnosis after the occurrence of symptoms, averaging around ten years for male and female patients grouped together.[40] Examining symptomatic females alone, this delay comes to an average of 16.3 years following the initial onset of symptoms.[12] Contributing to the diagnostic delay is the prevalence of misdiagnoses. Common misdiagnoses include but are not limited to rheumatological disease, arthritis, neuropsychological disease, and Raynaud's syndrome.[12] The suggestion of the presence of Fabry disease is most commonly contributed by nephrologists, dermatologists, ophthalmologists, or geneticists further highlighting a need for a multidisciplinary medical approach to Fabry patient care.[40]

Pedigree analysis and cascade screening of family members have served as useful tools for identifying at-risk individuals. In most cases, the proband will be an affected male when a diagnosis of Fabry disease is made in a new family, but identification of an index case allows for subsequent evaluation for individuals, including women, who have the potential to carry the family mutation. On average, approximately five family members are subsequently diagnosed with Fabry disease following diagnosis of the proband.[40,41]

A confirmatory diagnosis of Fabry disease is made using biochemical and molecular methods, although there are important nuances to the testing methods that differ between males and females.[33] In the past, confirmation of males suspected to have Fabry disease was made solely upon demonstration of absent or deficient α-galactosidase A activity in peripheral blood leukocytes and/or plasma. However, due to the potential presence of a common psuedodeficieny allele, D313Y, which results in reduced α-galactosidase A activity in plasma and slightly reduced levels in blood leukocytes, it is now recommended that a diagnosis be made only after both biochemical analysis and molecular testing of the *GLA* gene.[42] In contrasts, at-risk women with a suspected diagnosis of Fabry disease may only be confirmed with molecular testing of the *GLA* gene, by direct sequencing of the gene followed by deletion/duplication analysis. Examination by molecular methods is the only reliable method to provide a confirmation of diagnosis for women due to their heterozygous status, which can lead to low or normal α-galactosidase A activity, leading to false-negative or inconclusive results.[24,33,43,44]

2.1.1.5 Disease Management and Treatment

Fabry disease is a chronic and progressive condition in which multiple organ systems are affected. Therefore, management of the many manifestations of Fabry disease requires a multidisciplinary team of medical providers for affected individuals.[6,20] The recommended guidelines for clinical evaluations and frequencies of follow-up are detailed in Eng et al. 2006 for all adult and pediatric individuals with Fabry disease. In summary, general evaluations should be made on a semi-annual or annual basis supplemented with evaluations from nephrology, cardiology, neurology, ophthalmology, pulmonology, orthopedics, ENT, and gastroenterology as clinically indicated.[6]

The symptomatic manifestations of Fabry disease result from the accumulation of lysosomal GL3 throughout the body due to a deficiency of α-galactosidase A enzyme activity. By targeting this aberrant process, the primary treatment for Fabry disease was developed in the form of intravenous enzyme replacement therapy (ERT) of agalsidase alpha or beta, which are now considered the standard therapy to treat manifestations of Fabry disease. Prior to the development of ERT, treatment for Fabry disease was palliative and focused on symptomatic management only. ERT however, effectively decreases the levels of accumulated GL3 from the circulation and sites of substrate deposit such as the endothelium of the liver, skin, kidney, and the heart to improve patient health outcomes.[20,45] Therefore, it is important that independent evaluations by relevant specialists for each organ system to be made in order to monitor the efficacy of ERT in each individual.[45]

ERT treatment with agalsidase beta is delivered intravenously in biweekly intervals at 1mg/kg doses for most patients who receive it in the U.S.[20,46] Typically, the procedure is initiated in an outpatient setting to verify the safety of the procedure for each patient, after which it can be relocated and administered at the patient's home by a trained home care nurse. For older patients with disease manifestations, there are two goals of ERT. One of which is to curtail the progression of the disease and the other is to reverse underlying pathologic abnormalities and organ dysfunction caused by GL-3 accumulation. Current guidelines recommend that all adult male patients receive ERT regardless of their clinical presentation, as the symptoms of Fabry disease are well-known to progress over the lifetime of the individual. In younger patients, the goal of ERT is preventive in nature. Males at the age of 16 and younger are recommended to initiate ERT upon the development of symptoms or at the age of 10-13 years old if the child is asymptomatic. Women however, are advised to initiate ERT only upon the presentation of

progressing organ involvement or at the point of manifestation of significant symptoms such as chronic acroparesthesias resistant to conventional therapy, persistent proteinuria (>300 mg/24hrs), glomerular filtration rate (GFR) below 80 ml/min/1.73m^2, clinically significant cardiac involvement, a previous cerebrovascular accident or history of transient ischemic attacks, or ischemic changes on brain MRI.[6,20] Clinically, ERT has been demonstrated by multiple studies to have a significant improvement in Fabry-related pain and quality of life for the patient.[7,45,47,48] ERT in the pediatric population, both male and female, has also been demonstrated in the short term to have beneficial effects on the neurological outcomes of the disease by decreasing and preventing pain symptoms.[48] Despite the utility of ERT, it is still important to implement and maintain adjunctive therapies and close disease monitoring to manage the multiple aspects of the disease, especially for proteinuria, stroke monitoring, gastrointestinal stress, and depression.[33]

There has been a lack of consensus among clinicians regarding the efficacy of early initiation of ERT in the reduction and prevention of severe manifestations and clinical events (i.e. stroke, end-stage renal disease, cardiac arrhythmia). Some argue that because clinical manifestations of Fabry disease are the direct result of accumulation of GL3 and related glycosphingolipids, treatment should be initiated as early as diagnosis regardless of symptoms.[8,49] More recently, long-term studies have evaluated the benefit of prolonged ERT and the effects of ERT on clinically significant symptoms and health-related quality of life outcomes in patients. These studies have concluded that ERT reduces the frequency of major clinical events compared to control groups through a slower progression of disease manifestations. However, these studies also acknowledge the lack of findings supporting complete prevention and reversal of organ damage leading to the conclusion that earlier, pre-symptomatic,

intervention with ERT would be of greater benefit to the patient than later intervention.[7–10] In general, long-term application of ERT has the ability to delay the onset of both clinically significant events and mortality when initiated in the earliest stages of Fabry disease before the presence of organ damage.[8,50,51]

Many of the complex factors of Fabry disease have also been identified as having a negative impact on the psychological functioning of both male and female Fabry disease patients by acting as barriers to disease treatment, evaluation, and monitoring. Impactful factors identified in the literature include the demanding recommendations for clinical evaluations and treatment, conflicts with schedules, financial resources, medical insurance, fear and distrust in treatment, and risk of infusion reactions to ERT.[31,52] However, the existence of factors that create a unique burden in affected females remains unclear.

2.1.2 Psychosocial Issues Associated with Fabry Disease

Psychological issues are a commonly underappreciated and overlooked aspect of Fabry disease by providers. However, understanding these issues have the potential to provide insight to the existing barriers to optimizing treatment for affected patients. Individuals diagnosed with Fabry disease are at an increased risk for several mental health issues such as depression and anxiety, as well as social-adaptive functioning deficiencies compared to their healthy counterparts. Several studies on predominantly male Fabry patient populations have analyzed the contribution of various factors of Fabry disease and identified the chronic, unpredictable, life-limiting, and debilitating effects of the condition as significantly contributing towards an increase in the likelihood of clinical depression and other mental health issues in patients.[4,28,53] Deficiencies in social-adaptive behavior function directly correlate with these mental health issues and are

reflected by the higher rates of alcoholism, marital issues, unemployment, non-compliance with treatment, and suicide in Fabry disease patients.[28,31,54] Additionally, there is an added layer of psychological complexity resulting from receiving a genetic diagnosis which may further complicate the mental health status of patients with feelings of denial, anger, grief, survivor and parental guilt, blame, isolation, inability to cope, hopelessness, damage to self-esteem, changed relationship with family of origin, and a change in sense of identity.[4,55]

The symptoms of Fabry disease are well-known to negatively impact the day-to-day lives of those living with the condition in multiple ways. Chronic pain, fatigue, and exercise intolerance can limit the rate of physical activities of symptomatic patients to a sedentary lifestyle that may contribute to secondary health problems. Pain and fatigue, as well as embarrassment of visible disfiguring angiokeratomas in the genitalia region, can contribute to significant psychological distress and difficulties initiating and maintaining sexual relationships. Continuous severe neuropathic pain, which can only be alleviated by narcotic medications, can lead to substance dependence. Increased rates of alcoholism and suicide have also been reported as manifestations of poor social-adaptive functioning to the psychological and somatic facets of Fabry disease. ERT infusions can be disruptive and burdensome to the social lifestyle of patients. Furthermore, an increasing state of disability, awareness of a shortened lifespan, and the unpredictability of chronic symptoms such as pain crises and gastrointestinal dysfunction coupled with the experience of an extended diagnostic delay may lead to feelings of depression, becoming sullen, withdrawn, and fatalistic about the future and their own ability to be helped by medical science.[4,28,29,52]

2.1.2.1 Psychological Burden and Medical Quality of Life among Female Heterozygotes

Although affected by the same disease as men, an increasing amount of evidence suggests that women who are heterozygous for Fabry disease not only share many mental health manifestations and psychosocial burdens as their male counterparts, but also experience Fabry related psychosocial issues that are unique to their gender. Similar to what has been identified in predominantly male cohorts, a 2007 study by Wang et al., which focused specifically on the experiences of 44 heterozygous women, identified a high prevalence of depression and anxiety stemming from factors such as disease rarity, chronic fatigue, exercise-intolerance, and pain at prevalence levels comparable to that of affected males.[5] Another study on a cohort of 202 affected females published in 2006 by Street et al. concluded that there are significant reductions in quality of life parameters compared to both healthy women and populations of other chronic disease suffers, including rheumatoid arthritis and multiple sclerosis.[39]

The psychosocial burdens experienced uniquely by women have been attributed at least in part by disadvantages imposed by their devalued carrier status. The nature of X-linked conditions is that women carry a working copy of gene along with a mutation while men only carry a mutation, driving the misconception that Fabry heterozygous women are either asymptomatic or experience intermittent and mild symptoms of the disease. With Fabry disease this assumption is incorrect and so the misconception persists, leading to the under recognition of the presence and extent of disease related symptoms in women.[11] Additionally, misconceptions of carrier status may also drive women to fail to recognize their own disease risks as it may conflict with their own views of their health, especially when they do exhibit minimal symptoms themselves or compare themselves to much more severely affected men in their families.[17]

2.1.3 Barriers to Healthcare for Female Heterozygotes

Gender has been identified as being a major contributory factor to the formation of unique barriers to healthcare and treatment for heterozygous Fabry patients. A substantial gender inequality gap exists in healthcare treatment overall which can lead to disparities in how a chronic disease patient, such as one with Fabry disease, is treated, managed, and followed.[11,56] In the realm of healthcare, females have a history of being labeled by physicians as patients who are more problematic and less credible compared to male patients, resulting in reported health complaints by females being more likely to be attributed to psychosomatic origin or a potential mental health diagnosis when there is no objective evidence of the origin of the symptoms present.[57] Furthermore, the prevailing misconception that heterozygous females are not affected by Fabry disease has also been reported as contributing to the prevalence of disregard, disbelief, and dismissal of health related complaints by healthcare providers, perpetuating the barriers to optimal healthcare for female heterozygotes.[11] However, over corrective measures by physicians for the fallacy of devalued carrier status can be equally damaging to the quality of healthcare for heterozygotes. Two separate studies focusing on the experiences of women diagnosed with Fabry disease noted that in some cases, physicians had the tendency to attribute all of a patient's symptoms to Fabry disease.[11,17] The actions of both under and over attributing health complaints to Fabry disease have the dangerous potential to create barriers to communication between the provider and the patient and result in less than optimal delivery of healthcare, underscoring the importance of accurate communication between the provider and the patient about the potential origins of health ailments in a female with Fabry disease.

3.0 MANUSCRIPT

3.1 INTRODUCTION

Fabry disease is a rare X-linked lysosomal storage disorder caused by mutations in the galactosidase alpha (*GLA*) gene which encodes the enzyme α-galactosidase A[1]. Insufficient levels or functioning of this enzyme results in the progressive accumulation of a glycosphingolipid substrate, globotriaosylceramide (GL-3), throughout the vasculature endothelial cells of the body leading to multi-systemic manifestations.[2,3] Symptoms arising from the disease include manifestations in the renal, cardiac, neurologic, cerebrovascular, ophthalmologic, dermatologic, and gastrointestinal systems which are chronic and progressive in nature. Those affected with Fabry disease often succumb to life-limiting complications from renal insufficiency, central and peripheral disease of the nervous system, cerebrovascular, and cardiovascular disease.[2,3,12,24]

In the past, it was assumed that females were not at-risk for development of Fabry disease symptoms due to the fact that females possess a working copy of the *GLA* gene. However, it is now recognized that heterozygous women in fact, can experience clinical symptoms similar to their affected male counter parts, although with greater variability in clinical presentation, necessitating appropriate monitoring and treatment for the disease.[4,5] Nevertheless, the differences in the course of disease experienced by the Fabry affected female population

introduce new challenges for the medical providers caring for these individuals. Heterozygous females not only require a different method of diagnosis from their male counterparts, but the clinical care guidelines for initiation of therapies should be adapted to the needs of female heterozygotes as well. At present, a discrepancy exists between the recommendations for men and women despite the presence of evidence suggesting the need for equal treatment.[6–10,33] Several studies evaluating the effectiveness of primary Fabry therapy in both men and women have concluded that initiation of therapy should take place before the first signs of disease are present.[7–10] However, generalized guidelines for Fabry disease treatment recommend that initiation of enzyme replacement therapy (ERT) should take place by the age of 10 to 13 in males regardless of disease burden, whereas in females, initiation of ERT should only take place when significant clinical manifestations are present.[6]

Furthermore, it has been reported that regardless of recommendations from healthcare providers, heterozygous women frequently dismiss their own risk to develop significant Fabry-related manifestations and are not usually evaluated in the clinical setting unless they present with severe complications of the disease, suggesting the possible presence of barriers to treatment for female heterozygotes.[2,5] A study dedicated to investigating the potential reasons as to why this scenario occurs at such a high frequency identified that female heterozygotes face several disadvantages in the healthcare setting which may contribute to their lack of participation in their own healthcare. The study identified factors such as the uncommonness of Fabry disease, the prevailing misconception that female heterozygotes are unaffected carriers of the disease or only express mild symptoms, and the disparity between healthcare treatment of men and women in the context of limited objective evidence that create inherent disadvantages for women with Fabry disease, long before they present for their first appointment in the clinic.[11] In combination

with existing discrepancies in the disease guidelines, the inherent disadvantages heterozygous women face in the healthcare setting shape their own personal health beliefs and have the potential to raise barriers perceived by the patient which can hinder optimal disease management, monitoring, and treatment.

Although to date the clinical course of Fabry disease among heterozygous females has been extensively studied, the unique clinical experience and health beliefs of these women are only more recently beginning to come to light. Previous unpublished research from the Children's Hospital of Pittsburgh of UPMC focused on characterizing the health beliefs of female Fabry patients and identifying contributory factors to these beliefs through the patients' own report elicited in the forms of both interviews and surveys.[58] The findings of these studies identified that patients generally have an accurate understanding of the natural history of Fabry disease but demonstrated a decreased perception of personal susceptibility to the disease as well as feelings of anxiety and being overwhelmed in regards to the disease overall. In direct follow up to this research, this study focuses particularly on the clinical practices and beliefs of healthcare providers in order to investigate their contribution, or lack thereof, to the barriers perceived by female patients. This was achieved through using quantitative methods to ascertain and measure the clinical practices and opinions of genetic healthcare providers who work with adult female Fabry patients via an online survey.

3.2 METHODS

3.2.1 Participants

The participants for this study were comprised of healthcare providers who had experience caring for female patients who have been diagnosed with Fabry disease. Two providers who did not report themselves as having experience working with females diagnosed or at-risk for Fabry disease were excluded from the analysis in this study. Participants were recruited by an email advertisement containing a link to the online survey which was sent directly to select individual genetic counselors. Selected genetic counselors were chosen from the list generated by the Find a Genetic Counselor tool on the National Society of Genetic Counselors' website for each state due to their listed affiliations with an institution that is known to have an established treatment center for lysosomal storage disorders, as listed by the Massachusetts General Hospital's department of Neurology website. The responding recipients of this email were then asked to further distribute the recruitment letter to their colleagues who work with lysosomal storage disorders, thus maintaining anonymity of all participants. Once the email was received by potential participants, the anonymous online survey could be accessed by interested participants without further contact with the study administrators. Participants were not compensated for their involvement in the study.

3.2.2 Instrumentation

An online survey was administered through a web based link connecting participants to the 43 question study on the Qualtrics survey system. The survey's initial questions included non-

identifying demographic questions focusing on the type of practitioner, personal experience working with Fabry disease, and number of female Fabry disease patients seen. The next series of questions asked the participant's opinions on a variety of issues including the level of importance for initial evaluation in multiple clinical scenarios (i.e. degree of relatedness to a family member diagnosed with Fabry disease and expression of symptoms), clinical terms used regarding female Fabry patients, the clinical usefulness of published guidelines used by the participant, and the importance of initiation of primary therapy (ERT) given expression of various clinical symptoms. Finally, the survey asked participants to characterize the degree of compliance to recommended evaluation, monitoring, and treatment. The study questions were primarily single answer, multiple-choice response in format but some questions allowed for multiple response choices by the participant. The initial recruitment email script for this study described to participants that their informed consent was implied through their voluntary participation in the study by accessing the survey. The study was reviewed and approved by the University of Pittsburgh IRB committee under IRB number PRO16080196.

3.2.3 Data Collection

The web-based link to the study survey was accessible through the initial and follow-up recruitment emails. Initial contact via email requesting distribution of the survey was sent to 71 people, forty-three of which responded with agreement to receive and forward the recruitment email containing a link to the survey. Due to the nature of the recruitment methods for this study, a response rate could not be calculated. The survey could be accessed January, 2017 through mid-February 2017. A statement was included in the recruitment emails for the participant's reference emphasizing the voluntary nature of the study and that all answers recorded would

remain anonymous. Participants answered survey questions exploring their practices and beliefs regarding the clinical treatment of adult females diagnosed or at-risk for Fabry disease. Data collection took place after access to the online survey was closed.

3.2.4 Data Analysis

Data from the study survey was compiled and descriptive analysis for ordinal multiple choice responses were performed using Microsoft Excel. For inferential statistics, analysis was performed using the SAS analytical statistics software package. Analyses included Chi square tests between two variables to test for goodness of fit between observed and expected values for multiple survey questions (i.e. profession and a particular response). Due to the small sample size of the study, answers to survey questions represented by an ordinal scale were dichotomized into two groups for ease of analysis, (i.e. Very Important, vs Important, Somewhat Important, and Don't know/ Not sure) in assessing the odds ratios of holding a particular belief in a given scenario.

3.3 RESULTS

3.3.1 Participants

The survey was accessed by 58 participants, and by 50, yielding a completion rate of 86%. Incomplete surveys were included in the analysis due to the independence of each question analyzed. Two participant response sets were excluded because the participants did not meet

inclusion criteria for this study, which is being a professional who participates in the evaluation, management, and/or treatment of adult females either diagnosed or at-risk for Fabry disease. The participant sample included 39 genetic counselors, 12 physicians and 1 physician assistant (these two profession groups were pooled together for ease of calculating response count in this study), and 2 nurses plus 2 nurse practitioners (these two profession groups were also pooled together for calculating response count in this study). All physicians who participated in the study further identified their specialty in Genetics (n = 6), Medical Genetics (n = 4), or Biochemical Genetics (n = 2). Characteristics of the participants are summarized in Table 1. The survey contained three main topics: clinical evaluation, monitoring, and enzyme replace therapy (ERT) treatment. Each area included questions which asked for the participant's views on the level of importance placed on the given aspect of Fabry disease care, along with questions designed to investigate opinions on various aspects of each topic. Additionally, the survey incorporated questions that probed the participants' use of terms to describe their female Fabry patients and their perception of their patients' compliance with recommended clinical evaluation, monitoring, and treatment.

Table 1 *Study Participant Demographics*

	Physicians and Physician Assistants n = 13 (23%)	CRNPs and RNs n = 4 (7%)	Genetic Counselors n = 39 (70%)
Experience			
<1 year	0 (0%)	1 (25%)	6 (15%)
1 to <5 years	3 (23%)	2 (50%)	27 (69%)
5 to <10 years	1 (8%)	1 (25%)	2 (5%)
10+ years	9 (69%)	0 (0%)	4 (10%)
# Pts personally seen			
<5 females	7 (54%)	1 (33%)	24 (62%)
5-10 females	4 (31%)	1 (33%)	8 (21%)
11-20 females	1 (8%)	1 (33%)	4 (10%)
<20 females	1 (8%)	0 (0%)	3 (8%)
# Pts treated with ERT			
No females	2 (18%)	1 (33%)	5 (14%)
<5 females	6 (55%)	1 (33%)	16 (46%)
5-10 females	2 (18%)	0 (0%)	5 (14%)
11-20 females	1 (9%)	1 (33%)	6 (17%)
<20 females	0 (0%)	0 (0%)	3 (9%)

3.3.2 Clinical Evaluation

The clinical evaluation questions included in the survey asked the participants about their views regarding the level of importance of an initial clinical genetics evaluation for an adult female based on several scenarios which included different combinations of risk levels of inheriting Fabry disease and presentation of symptoms. These scenarios included (1) A reportedly asymptomatic woman with a family history indicating she has inherited Fabry disease (Example: Affected father), (2) A reported asymptomatic woman with a family history indicating she is at 50% risk to have inherited Fabry disease (Example: Affected brother), (3) A reportedly

asymptomatic woman with a family history indicating she is at 25% risk to have inherited Fabry disease (Example: Affected maternal uncle), (4) A woman with a reported history of myocardial infarction and a family history indicating she is at 50% risk to have inherited Fabry disease (Example: Affected brother), (5) A woman with a reported history of myocardial infarction and a family history indicating she is at 25% risk to have inherited Fabry disease (Example: Affected maternal uncle) (6) A woman with a reported history of left ventricular hypertrophy and burning pain in her hands and feet with no known family history of Fabry disease. Responses to each scenario were counted and compared, see Figure 1. In general, participants were in agreement that in the majority of the provided scenarios, an initial clinical genetics evaluation was "Very important". In one scenario however, where an asymptomatic woman with a family history indicating that she is at a 25% risk to have inherited Fabry disease, the participant population was divided, ranking the need for initial clinical genetics evaluation as either "Important" or "Somewhat important".

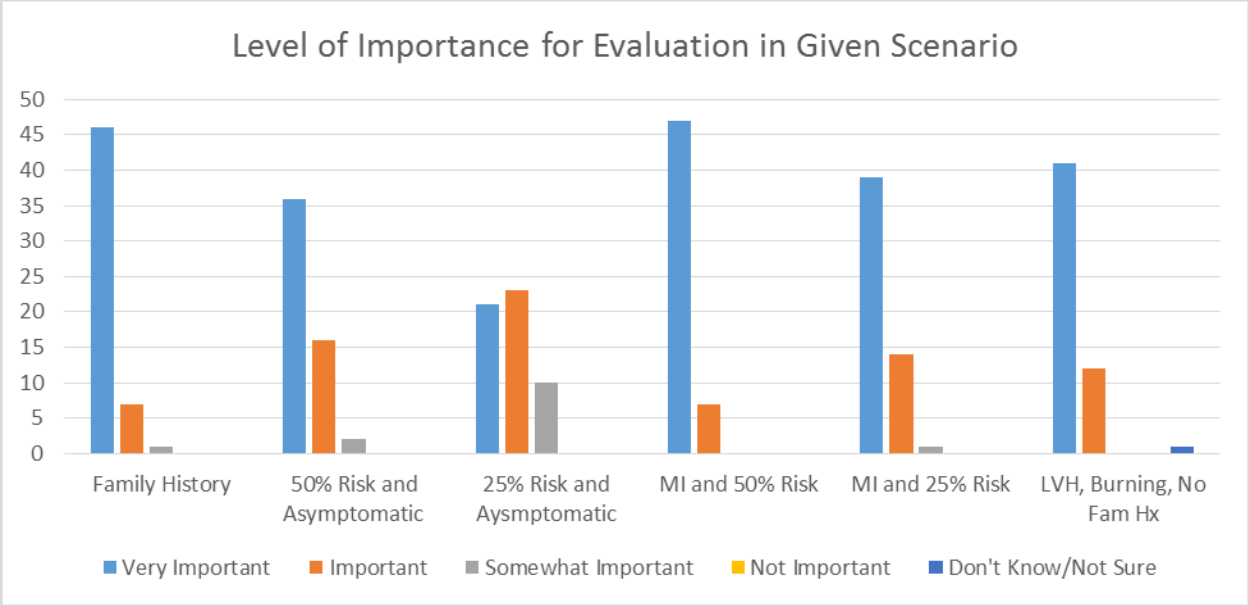

Figure 1 *Responses to the level of importance placed on an initial clinical genetics evaluation for an adult woman in six different scenarios*

In order to investigate and identify the potential influence of experience and profession on the observed response behavior for this cluster of questions, the response categories for these questions were dichotomized into two groups, "Very Important" and all other answers. Chi square analyses were utilized to investigate if participant number of years of experience working with Fabry patients or their profession predicted higher views of importance for an initial clinical genetics evaluation. For ease of analysis, reported years of experience was dichotomized into those who have less than five years of experience and those who have five years or more, and profession was dichotomized into genetic counselors and all others. Even though the analysis did not result in any tests that were significant, it was found that those with five years or more experience had increased odds of 1.06 to 2.85 times more to rate the importance of clinical monitoring as "Very important" for each scenario ($p = 0.757$, $p = 0.833$, $p = 0.947$, $p = 0.948$, $p = 0.768$, $p = 0.210$). When testing for profession, neither significance nor signs of potential

correlation were identified for the scenarios (p = 0.848, p = 0.521, p = 0.182, p = 0.960, p = 0.157, p = 0.264). Results are summarized in Table 2.

Table 2 *Chi Square Analysis for Initial Evaluation Scenarios*

		Experience				Profession			
Scenario	Overall Total Very Important	% <5 Years Experience say Very Important	% ≥5 Years Experience say Very Important	OR Point Estimate	95% Confidence Interval	% Other Professions say Very Important	% Genetic Counselors say Very Important	OR Point Estimate	95% Confidence Interval
A reportedly asymptomatic woman with a family history indicating she has inherited Fabry disease (Example: Affected father)	46 (85%)	84.21%	87.50%	1.312	0.235-7.323	86.67%	84.62%	0.846	0.151-4.745
A reported asymptomatic woman with a family history indicating she is at 50% risk to have inherited Fabry disease (Example: Affected brother)	36 (67%)	65.79%	68.75%	1.144	0.327-4.000	60.00%	69.23%	1.5	0.436-5.166
A reportedly asymptomatic woman with a family history indicating she is at 25% risk to have inherited Fabry disease (Example: Affected maternal uncle)	21 (39%)	31.58%	56.25%	2.785	0.838-9.261	53.33%	33.33%	0.438	0.130-1.472
A woman with a reported history of myocardial infarction and a family history indicating she is at 50% risk to have inherited Fabry disease (Example: Affected brother)	47 (87%)	86.84%	87.50%	1.061	0.183-6.134	86.67%	87.18%	1.046	0.180-6.081
A woman with a reported history of myocardial infarction and a family history indicating she is at 25% risk to have inherited Fabry disease (Example: Affected maternal uncle)	39 (72%)	71.05%	75.00%	1.222	0.323-4.627	86.67%	66.67%	0.308	0.060-1.572
A woman with a reported history of left ventricular hypertrophy and burning pain in her hands and feet with no known family history of Fabry disease	41 (76%)	71.05%	87.50%	2.852	0.554-14.688	86.67%	71.79%	0.392	0.076-2.027

3.3.3 Clinical Monitoring

The clinical monitoring questions elicited views regarding Fabry disease related monitoring. Participants were asked to rank their view on the level of importance they place on clinical monitoring, (e.g. urine protein excretion every 6 months, echocardiogram annually, brain MRI every 2-3 years, etc.) to the overall management of an adult female with Fabry disease. Responses were totaled, revealing a general consensus among participants that clinical monitoring was considered “Very important” or at least “Important”, see Figure 2a. Participants were also asked if female heterozygotes should be monitored as frequently as hemizygous males. Here, a divide in viewpoints was present among participants, where 12 participants responded with “Yes, in all cases” and 37 participants responded with “Yes, in some cases”, see Figure 2b.

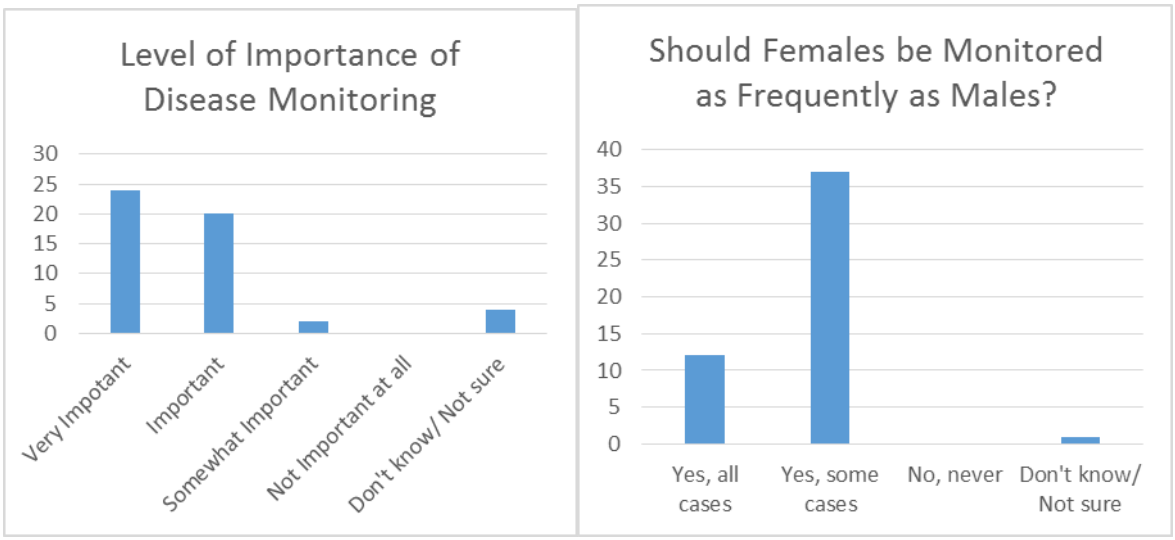

Figure 2 *(A) Regarded importance for disease monitoring in females and (B) monitoring frequency compared to males*

To decipher any relationships between participant years of clinical experience with Fabry disease and views of clinical monitoring frequency for female patients as compared to males, Chi square analysis was utilized revealing that participants with five years or more experience had a 67% increase in odds of to view the importance of clinical monitoring for female patients as "Very important" compared to those with less than five years of experience, however the finding did not reach significance (p = 0.4217). Additionally, compared to participants with five years or more experience, participants who had less experience were found to be at a 26% decreased likelihood of stating that female patients needed to be followed as frequently as males in all cases (p = 0.675). Investigating the effects of profession, physicians and nurses together compared to genetic counselors were found to be 40% less likely (OR = 0.6) to feel that the importance of clinical monitoring was "Very important" (p = 0.422). Physician and nurse participants were also found to be 22% less likely to state that female patients should not be monitored as frequently as male patients in all cases (p = 0.753). Chi square analysis is outlined in Table 3.

Table 3 *Chi Square Analysis for Clinical Monitoring Scenarios*

Scenario	Total Very Important	% <5 Years Experience say Very Important	% ≥5 Years Experience say Very Important	OR Point Estimate	95% Confidence Interval	% Other Professions say Very Important	% Genetic Counselors say Very Important	OR Point Estimate	95% Confidence Interval
How important do you believe frequent clinical monitoring is to the overall management of an adult female with Fabry disease?	24 (48%)	44.44%	57.14%	1.667	0.479-5.794	57.14%	44.44%	0.6	0.173-2.086
	Total "Yes, all cases"	**% <5 Years Experience say All Cases**	**% ≥5 Years Experience say All Cases**	**OR Point Estimate**	**95% Confidence Interval**	**% Other Professions say All Cases**	**% Genetic Counselors say All Cases**	**OR Point Estimate**	**95% Confidence Interval**
Do you believe adult females with Fabry disease should be clinically monitored as frequently as adult males with Fabry disease?	12 (24%)	77.14%	71.43%	0.741	0.182-3.011	78.57%	74.29%	0.788	0.179-3.477

When asked about their knowledge of recommended intervals for follow up evaluations, participants disagreed about the interval to follow up with symptomatic females, although there was a strong consensus that asymptomatic females be re-evaluated every 12 months (Figure 3). Factors cited by participants that could influence their decision regarding the timing of clinical monitoring included medical history of the patient, the patient's ERT treatment status, or uncertainty of the interval.

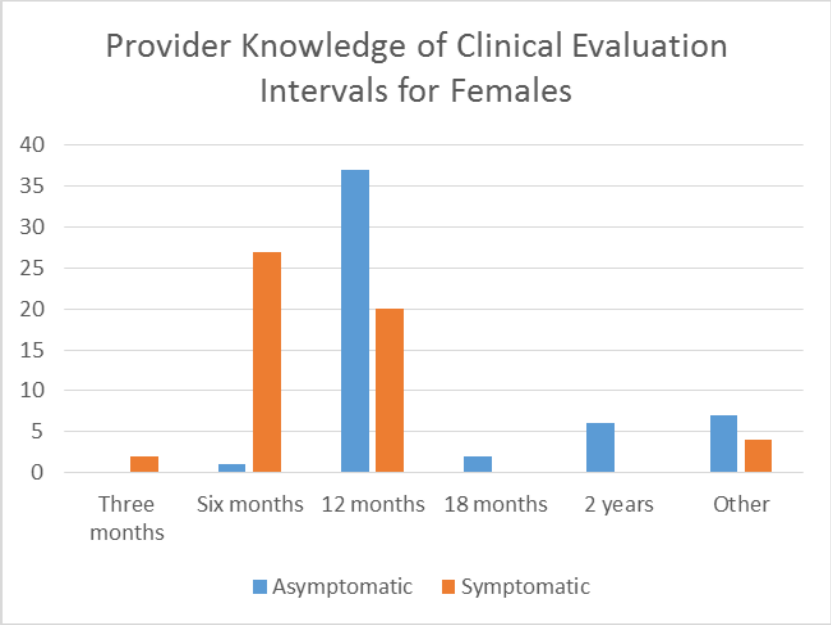

Figure 3 *Responses to the frequency of follow up evaluation by a physician knowledgeable of Fabry disease given an asymptomatic or symptomatic female patient*

Participants were also asked to identify the resources they used for guidance when making decisions regarding clinical monitoring for both male and female patients. Although the differences were small and not significant, likely due to the low power of this study, a pattern can be seen in the responses where published literature and industry guidelines were cited more often for males and personal experience was cited more often for females, see figure 4a. Participants were then asked in the next question to state the level of usefulness they perceived of the resources to which they referred to in the previous question. For this question, approximately one-third (35.3%) of participants indicated that the resources they utilized were "Very beneficial", see figure 4b.

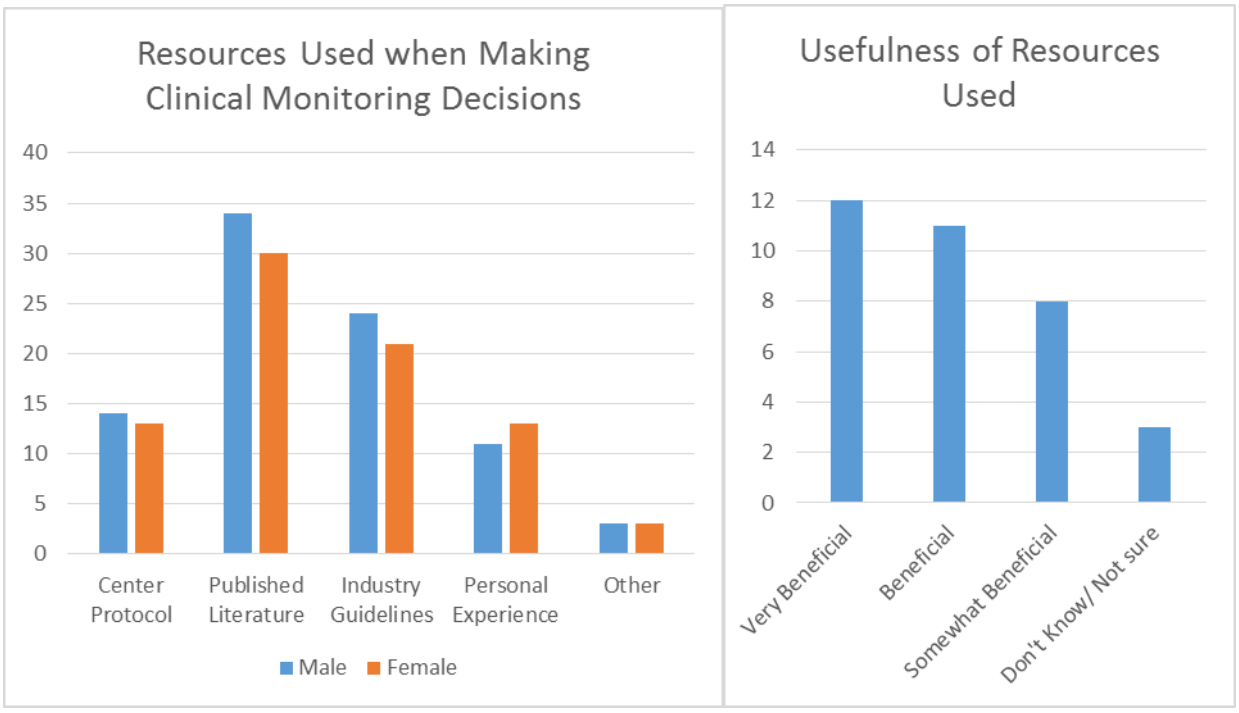

Figure 4 *(A) Various informational resources were used by participants in making clinical monitoring decisions and (B) usefulness of those resources*

3.3.4 Enzyme Replacement Therapy Treatment

Views surrounding initiation of ERT was the final of the three main topics of the survey. To assess participant views in regards to making the decision to initiate ERT in a female patient, the survey included questions containing four scenarios, each describing a single clinical symptom in a female patient known to have Fabry disease, (e.g. chronic and disabling gastrointestinal dysfunction, pulmonary involvement, abnormal blood pressure regulation during exercise testing, and generalized fatigue and malaise) and asked if the participant viewed the symptom as a sole indication to initiate ERT. Figure 5 displays participant responses for this cluster of questions. In the cases of GI dysfunction and pulmonary involvement, participants generally agreed that these were symptoms that would indicate the initiation of ERT in some, but not all,

cases. Abnormal blood pressure regulation during exercise testing totaled the lowest number of responses for "Yes, in all cases" and "Yes, in some cases" and the highest frequency of responses for "Don't know/Not sure" compared to the other three scenarios, although the response frequencies were again not significant. Generalized fatigue and malaise for initiation of ERT displayed the greatest level of disagreement among participants and was also the scenario that received the highest frequency of "No, never".

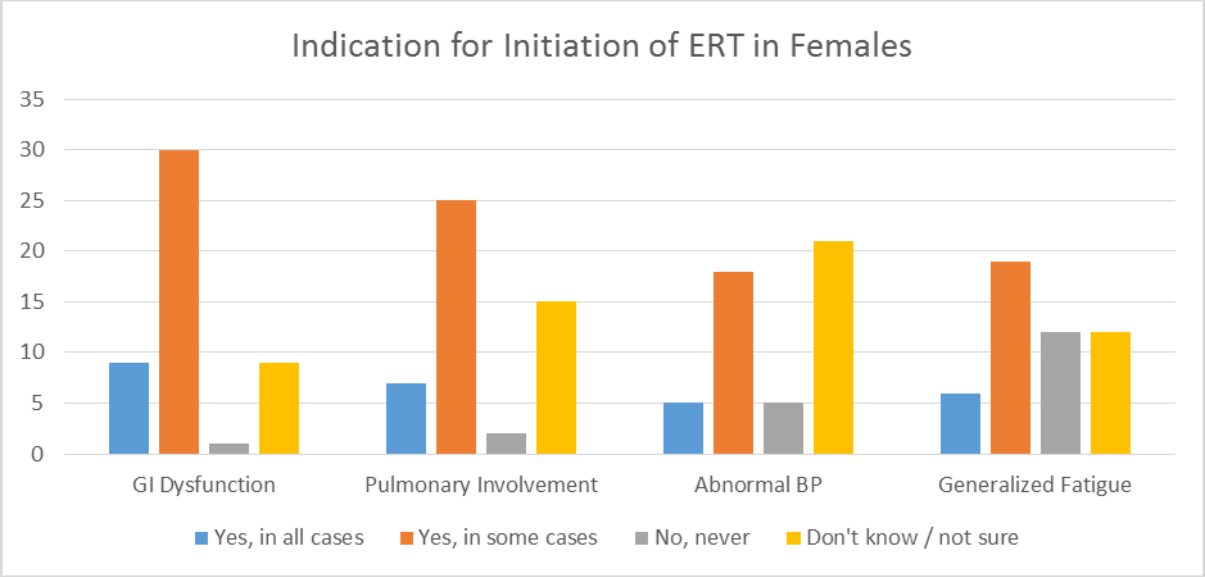

Figure 5 *Responses to a provided clinical scenario as the sole indication for initiation of ERT in females with Fabry disease*

Evaluating the odds of saying that initiation of ERT would be considered as "Yes, for all cases" by level of experience found that in all scenarios but the GI dysfunction, those with more experience had a 2.16 fold increase in the odds of saying that initiation of therapy should be a sole consideration for initiating ERT ($p = 0.727$, $p = 0.949$, $p = 0.657$, $p = 0.499$), see Table 4. In fact, in the case of pulmonary involvement, 100% of those with five years of experience or greater said that initiation of ERT should take place in all cases. Running the same evaluation for

profession, a similar phenomenon was not identified ($p = 0.226$, $p = 0.999$, $p = 0.555$, $p = 0.952$). This analysis found that genetic counselors only had a 78% increase in odds of saying that initiation of ERT should take place in all cases compared to all other professions grouped together in the scenario of generalized fatigue, see Table 4.

Table 4 *Chi Square Analysis for Initiation of Enzyme Replacement Therapy Scenarios*

		Experience				Profession			
Scenario	Overall Total Very Important	% <5 Years Experience say "Yes, all cases"	% ≥5 Years Experience say "Yes, all cases"	OR Point Estimate	95% Confidence Interval	% Other Professions say "Yes, all cases"	% Genetic Counselors say "Yes, all cases"	OR Point Estimate	95% Confidence Interval
Do you believe chronic, disabling gastrointestinal dysfunction is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult female with Fabry disease?	9 (18%)	82.86%	78.57%	0.759	0.161-3.574	92.86%	77.14%	0.26	0.029-2.300
Do you believe pulmonary involvement is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult female	7 (14%)	80%	100%	<0.001	<0.001->99.99	85.71%	85.71%	1	0.170-5.878
Do you believe abnormal blood pressure regulation during exercise testing is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult female with Fabry disease?	5 (10%)	88.57%	92.86%	1.677	0.171-16.482	85.71%	91.43%	1.778	0.264-11.984
Do you believe generalized fatigue and malaise is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult	6 (12%)	85.71%	92.86%	2.167	0.230-20.423	100%	82.86%	<0.001	<0.001->99.99

Regarding resources referred to when making decisions concerning the initiation of ERT in female patients, participants who stated involvement in the decision making process were asked if they specifically utilized the clinical guidelines outlined by the Eng et al. (2006) or other literature, see Figure 6a.[6] The result indicated that 58.9% of participants involved in ERT decision making specified that they referred to the Eng article in at least some cases and 31.4% participants involved in ERT decision making specified that they utilized other resources, the two categories were not mutually exclusive. Other sources cited by the participants included center protocols and/ or personal experience, the Genzyme Fabry registry, and other more recently published literature such as Biegstraaten et al. 2015 and Weidemann et al. 2012.[59,60] Participants who did state they referred to the 2006 Eng et al. paper were then asked a follow up

question asking them to rate the degree of helpfulness they found the guidelines in the Eng paper to be for making decisions regarding initiation of ERT for their female patients. Approximately one-fifth of responding participants (18.8%) viewed the guidelines to be "Very helpful", see figure 6b.

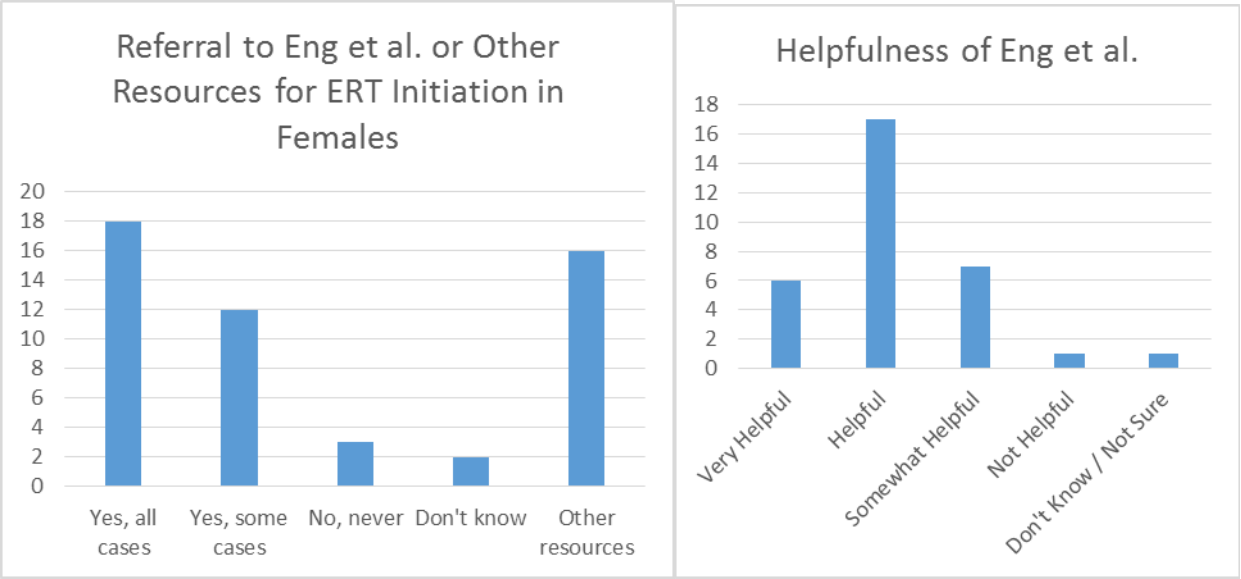

Figure 6 *(A) Referral to 2006 Eng et al. when making decisions regarding the initiation of ERT in female patients and (B) the level of helpfulness of 2006 Eng et al. for this purpose*

3.3.5 Terminology and Compliance

To further characterize the practices and beliefs of providers caring for female patients with Fabry disease, the survey included questions to explore participants' preferred terms for describing both asymptomatic and symptomatic patients. Participants were asked to select which terms they use to describe both patient types and/or provide alternative terms which they utilize. Response categories included "Fabry female", "Carrier", "Female Heterozygote", "Asymptomatic/Symptomatic Female", or "Other". Although there is not enough power to show

significance, differences can be seen between the asymptomatic and symptomatic categories which are conserved across provider groups, see Figure 7. Use of "Fabry Female" was selected at a higher frequency for describing symptomatic patients compared to asymptomatic patients while use of "Carrier" and "Female Heterozygote" displayed the opposite pattern.

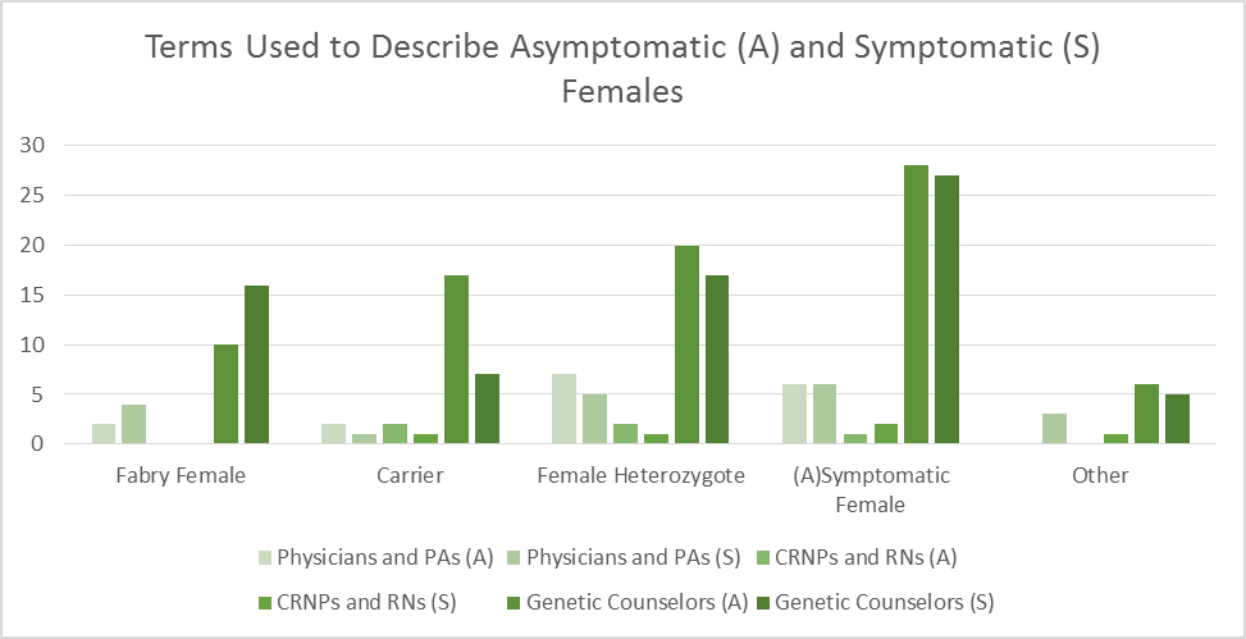

Figure 7 *Frequency of responses to use of descriptive terms to describe female patients that are asymptomatic (A) and symptomatic (S) by provider category*

Lastly, providers were asked to state the level of which they perceived their patient population to comply with recommended clinical evaluations, monitoring, and treatment. Figure 8 depicts participant responses where 22.4% of participants described their patient population to be "Highly compliant" with clinical evaluations, and 20.4% of participants described their patient population to be "Highly compliant" with clinical monitoring. Conversely, 43% of participants declared their patient population to be "Highly compliant" with ERT treatment.

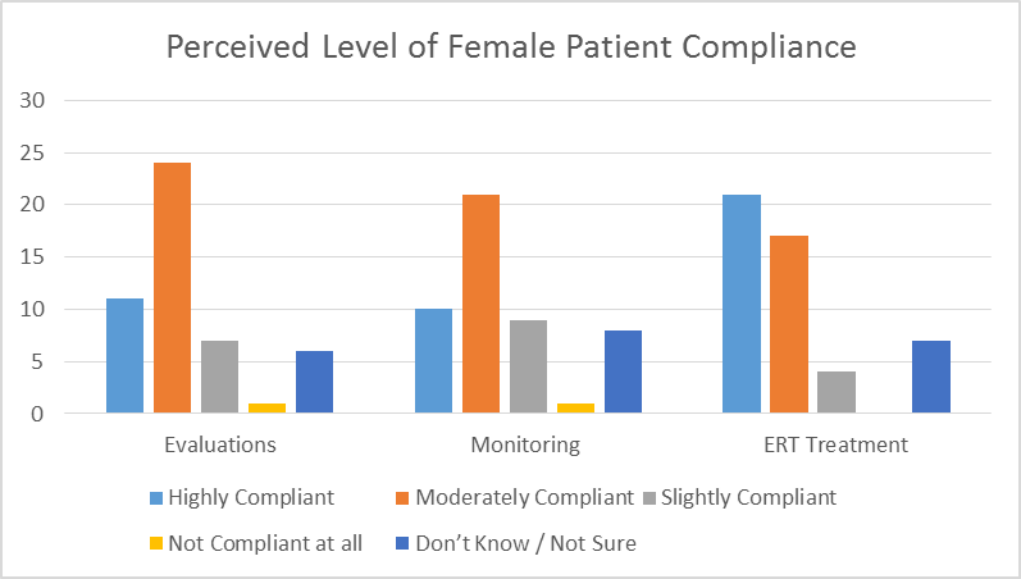

Figure 8 *Frequency of responses describing participants' perceptions of their female patients' level of compliance with recommended clinical evaluation, monitoring, and treatment regimens*

3.4 DISCUSSION

3.4.1 Practice Implications for Genetic Counselors

The purpose of this study was to characterize the clinical practices and beliefs of healthcare providers involved in the care of adult female patients with Fabry disease in order to investigate the possible barriers which can hinder optimal disease management, monitoring, and treatment. The findings highlight a lack of consensus among genetics healthcare providers regarding clinical practice in several areas of Fabry-related care. Notably, participants with five years or more experience differed, although not significantly, from those with less experience in their opinions regarding the importance of all three topics of study (i.e. clinical evaluation, monitoring, and treatment). Overall, these findings highlight that clinician behavior is varied and

therefore raise the possibility that clinician behavior may have the potential to influence the barriers women with Fabry disease perceive and experience, in directions both positive and negative.

During the clinical decision making processes, problems for healthcare providers may arise from the reduced penetrance and wide clinical variability of Fabry disease manifestations in female heterozygotes, and from the conflicting information in the literature regarding best clinical practices to care for these patients. For example, it is estimated that approximately 60-70% of heterozygous females experience at least one symptom attributable to Fabry disease with an average age of onset at 9 years old.[4,26,27] However, whether symptoms will be severe or mild in a given individual is a factor that cannot be reliably predicted by phenotype/genotype correlations or by studying other members in the family.[22] As a result of this uncertainty, the clinical practice guidelines outlined in Eng et al. 2006 for adult patients with Fabry disease advises that enzyme replacement therapy (ERT) not be initiated in female patients unless an individual presents with progressing organ involvement or manifestations of significant clinical symptoms such as acroparesthesias resistant to conventional therapy, persistent proteinuria, or clinically significant cardiac involvement.[6] Conversely, these same guidelines advise initiation of ERT in all hemizygous males, regardless of their clinical presentation, due to the knowledge that over the individual's lifetime, accumulating glycosphingolipids will result in progressive organ involvement if left untreated.[6]

In practice, there are trade-offs to be balanced when making the decision to initiate ERT in a patient, as well as considerations of the expectations and goals of the patient and provider for the use of ERT. For males, the clinical course of progression of Fabry disease is well known to reach medically significant outcomes when left untreated and therefore ERT is initiated early in

most patients' lives, despite its costs and burdens, as a form of preventive healthcare to reduce the morbidity and mortality of the disease. However, in the early years of a female's life, it is unknown whether she will develop any significant clinical manifestations or if she will live her life relatively unaffected by the disease. In the context of ERT initiation in female patients, a clinician must weigh the burden and cost of biweekly ERT infusions on the patient against the burden of the patient's clinical manifestations, thus increasing the likelihood of a delay of ERT initiation in contrast to males. In comparison, according to the guidelines outlined by 2006 Eng et al., males should receive ERT in order to prevent the occurrence of Fabry symptoms, and women should receive ERT as a means to halt disease progression that has already begun to manifest.

The findings of this study contribute evidence that the clinical practices among genetic healthcare providers involved in the care of patients with Fabry disease are not consistent. This was made evident by the differing, although non-significant, response patterns of distinct professional groups and experience levels among participants. Additionally, this observation may result as a byproduct from the lack of consistency between published guidelines and current literature or other unidentified factors. Importantly though, this inconsistency may in turn negatively impact female patients by contributing to their perceived barriers to participation in clinical evaluation, monitoring, and treatment thus limiting optimal disease treatment. If variability in clinical practice and barriers perceived by heterozygotes are truly linked, it can be predicted that a greater consistency among provider practices may help in reducing existing barriers for female patients and subsequently improve their clinical outcomes. Genetic counselors, having specific training in the psychosocial implications of disease, are well equipped to address this issue and should utilize their skills by integrating this newfound

knowledge of the potential contributions of variability in genetics provider practice to the perceived barriers to Fabry disease as part of their counseling to better meet the needs of the patient. With knowledge of how external factors may influence a patient's decision making and behaviors, genetic counselors have the tools to formally counsel female patients regarding the psychosocial impacts of the barriers related to Fabry disease, and open a dialogue with the patient about finding strategies to reduce the impact of these barriers and ultimately improve the healthcare outcomes for these patients.

3.4.2 Clinical Evaluation

An initial clinical evaluation is an essential first step in establishing a diagnosis and commencing treatment for a patient affected with Fabry disease. Yet establishing a diagnosis in a patient that lacks a family history of the disease can be exceptionally difficult, as many of the symptoms of the disease are not specific to Fabry disease, often leading to a misdiagnosis or a 'diagnostic odyssey'.[40] To assist with guiding providers in the initial evaluation of Fabry disease, Laney et al. (2013), developed guidelines that highlight what combination of symptoms should trigger an initial evaluation for Fabry disease in a patient that lacks a family history.[33] However, the findings of the initial evaluation scenario questions of this study suggest that all providers may not follow the 2013 guidelines when making decisions regarding initial evaluations because the guidelines suggest that any woman with a family history of disease should be evaluated. For patients who do not report a family history, it is more likely that evaluations are often initiated by providers savvy enough to recognize the potential of the rare genetic disorder as an explanation for their patient's ailments, rather than the provider having specific knowledge of the symptoms in the guidelines.

This study found that even in scenarios where a patient does present with a family history, the importance of a clinical evaluation may not always be regarded as very important by genetics healthcare providers. Although this study was not powered for significance, a directional pattern in response frequency can be seen showing that with decreasing levels of inheritance risk, asymptomatic individuals are perceived to be in less of an urgent need of evaluation, see Figure 1. This is to be expected in context of the usual occurrences within Fabry care, where in many clinics female patients are often not evaluated, monitored, or treated when they have inherited a mutation but are not expressing symptoms of the disease.[2,5] Chi square analysis did, however, identify an association in views of importance as it relates to the experience level of participants, although the results of the test did not reach significance. Participants who indicated that they had five or more years of experience were more likely to view the importance of clinical monitoring as "Very Important" compared to those with less than five years of experience, for all given scenarios, (Table 2). This finding although interesting, was expected because of the expectation that providers who have more experience would have a greater understanding of the potential for disease progression in females.

3.4.3 Clinical Monitoring

To monitor the progression of disease, determine the need and proper timing of initiation of ERT in Fabry patients, or to evaluate the efficacy of ERT on slowing disease progression, clinical monitoring of Fabry patients can serve as a useful tool for clinicians. On this topic, study participants generally agreed that the role of clinical monitoring in female patients with Fabry disease was very important (Figure 2a), although participants generally disagreed upon the proper interval which monitoring should take place in symptomatic females (Figure 3).

Interestingly, disagreement on the interval of monitoring was not seen for asymptomatic female patients, as a strong majority of participants cited annual monitoring as the appropriate interval for this population.

The 2006 Eng et al. guidelines state that symptomatic females be evaluated every 6 months.[6] The variation observed in what participants perceived to be the interval necessary to monitor symptomatic female patients, ranging from more frequently to as frequently as monitoring in asymptomatic female patients, is somewhat surprising given that the guidelines address this issue. With this in mind, these findings suggest that a portion of genetics healthcare providers may be drawing from their professional judgment and experience or they may be factoring context that was not provided in the survey when making decisions regarding the timing of intervals for evaluation of a symptomatic female patient.

When asked to make the comparison to male patients, some participants stated they believe that female patients should be monitored as frequently as male patients in all cases but others stated they believe that female patients should be monitored as frequently as males in only some cases (Figure 2b). Eng et al. guidelines state that female patients only require clinical monitoring as frequently as males when they are symptomatic.[6] Further analysis revealed that in the group of participants who stated that clinical monitoring in females should be as frequent as monitoring in males, there was an overrepresentation of participants who had more experience within the field of Fabry disease, see Table 3. Although not significant, this is a pattern of responses that was expected, as providers who have spent more time in the field would have a higher probability of observing the capacity of a symptomatic female heterozygote to be affected to the same degree as a male patient. Generally speaking, the more experienced a genetics

provider is, the more likely it would be expected that the provider would treat male and female Fabry patients equally, despite the recommendations of clinical guidelines.

Personal experience was also found to be cited as a resource utilized by the participants more frequently when making decisions regarding the interval for disease monitoring for a female patient than for a male patient. Again, the response frequencies were not significant, but the wide variability of disease severity in females may provide an explanation for this pattern. For instance, providers may refer to their personal experience when making the judgment to recommend an increased regimen of clinical monitoring for female patients with differing medical histories, even though they may all be symptomatic by definition.

Despite the clinical utility of consistent disease monitoring, several female patients do not receive adequate follow up unless they present with serious complications of the disease, regardless of the recommendations made by their providers, due to the fact that many female patients deny their own susceptibility to manifest clinically significant symptoms.[2,5] By recommending a schedule of clinical monitoring appointments for asymptomatic female patients that are as frequent as for male, or symptomatic female patients, it may send the message to asymptomatic female patients that their risk of developing significant symptoms has the potential to be as high as it is for male patients which may contribute to improvement in female attendance to their Fabry clinical monitoring appointments. Even so, a discussion between the provider and the female patient should take place when formulating a plan for clinical monitoring in order to identify any misconceptions about the patient's own susceptibility to the disease.

3.4.4 Enzyme Replacement Therapy Treatment

Intravenous enzyme replacement therapy (ERT) with agalsidase beta (Fabrazyme, Genzyme, Sanofi Inc.) was approved in 2003 by the Food and Drug Administration (FDA) and is currently the only approved treatment for Fabry disease within the United States. Regarding the timing for initiation of ERT in a patient, Fabry disease practice guidelines differ in their recommendations. Eng et al. (2006) states that ERT initiation in female patients should take place upon development of significant clinical manifestations, whereas guidelines published by Laney et al. in 2013 state that initiation of ERT should be determined based on the clinical judgement of a metabolic specialist in conjunction with the patient.[6,33] Lack of strict specificity, as well as room for professional interpretation in the practice guidelines, are likely explanations for the wide range of responses observed for study questions eliciting participant opinions on when to initiate ERT in a hypothetical scenario involving a female patient. For each scenario, relatively few participants stated that they would consider the scenario to be the sole reason for initiating ERT in a female patient in all cases. In fact, the highest response counts were seen for considering the given scenario as a reason for initiating ERT in just some cases and for being uncertain if they would consider the scenario as a sole reason for initiating ERT (Figure 5). It is possible that individual providers interpret the severity of each clinical symptom differently or that the participants may be using context not provided by the survey, such as their own experience with how patients react psychosocially to each clinical symptom. For example, studies examining the day-to-day psychosocial burden of Fabry symptoms on patients have found that in some cases even though the manifestations alone may not be severe, chronic symptoms such as GI dysfunction or pain and fatigue may contribute to secondary health problems or mental health issues like depression and anxiety.[4,28,52] It is possible that some providers integrate the potential

impact of these secondary health issues when evaluating the need for initiation of ERT in a patient.

Another possible explanation for the range of responses observed in questions regarding initiation of ERT in the given hypothetical scenarios could be the rate of use of a particular set of guidelines by the participants. This study identified that only about two-thirds of the participants who were involved in the decision to initiate ERT in a patient referred to the 2006 Eng et al. guidelines in at least some cases (Figure 6a) and of these participants, only about one-fifth of them found the guidelines to be "Very helpful" (Figure 6b). Participants who do not find the guidelines to be very helpful may turn to other sources for guidance as they engage in clinical decision making for initiating ERT in their patients.

Grouped together, participants who reported five years of experience or more were found to differ from those who had less experience regarding their views on considerations they place on initiation of ERT in the provided hypothetical scenarios. Chi square analysis revealed that in cases of pulmonary involvement, abnormal blood pressure regulation, and generalized fatigue and malaise those with more experience in the field were more likely to view the single symptom as a sole consideration to initiate ERT in a female patient (Table 4). As previously discussed, this finding can be explained by the available guidelines and the recent studies revealing the level of impact the symptoms of Fabry disease may have on female patients. Thus, these providers may be referring to their best clinical judgment when making the decision or they may have more familiarity with the level of burden these symptoms may impose on a patient compared to those who do not have as many years of experience in the field of Fabry disease.

3.4.5 Terminology

This study examined terms used by participants in order to explore the potential existence of factors that could contribute to the barriers of engaging in clinical evaluation, monitoring, and treatment for women with Fabry disease. Terms that were found to be used more frequently to describe asymptomatic female patients by participants were “carrier” and “female heterozygote” and the term that was preferred to describe symptomatic female patients was “Fabry female”, see Figure 7. Nomenclature used for describing female Fabry patients is important because it can hold the potential for miscommunication between the patient and the provider regarding the patient’s potential for developing symptoms of the disease. For example, the term “carrier” does not accurately reflect the clinical status of female patients and may even lead to a delay in clinical evaluation and treatment, thus some authors have called for the cessation of the use of the term.[5,24]

3.4.6 Compliance

In agreement with what has been previously been reported in the literature, the participants of this study reported a lack of compliance for clinical evaluation and monitoring in their female patient population.[2,5] Non-compliance with Fabry-related care has been correlated with deficiencies in social-adaptive functioning, depression and anxiety arising from the every-day burden of the disease, and the psychologically complex feelings that may arise when an individual is coping with a genetic diagnosis.[4,28,31,55] However, in regards to ERT, the rate of participants reporting their patient population being “Highly compliant” is approximately double the rates reported for the other two categories. This may be because patients who receive ERT

may have symptoms that are more severe than average, thus increasing the patient's motivation to comply with a treatment regimen, or that these patients may not be as susceptible as other patients to being impeded by barriers to receiving initial evaluations or monitoring, or some combination of both explanations. Yet, in order to determine the validity of these explanations, further studies would be required.

3.4.7 Research Recommendations

The purpose of this study was to explore the clinical practices and beliefs of healthcare providers involved in the care of adult female Fabry patients in order to identify factors originating from provider clinical practices that could contribute to a female patient's perceived barriers to engaging in Fabry-related preventative health behaviors. By identifying these contributory factors, effective action can be taken to increase awareness of the contribution to barriers made by these factors and to improve the health outcomes of female Fabry patients overall. The results of this study suggest that all providers do not practice Fabry-related care in the same way. In each category of exploration, patterns in responses were identified which differed by provider or experience level, although these patterns were not found to be significant. A study incorporating a larger and more equally representative participant population would be useful in determining if the observed patterns of response behavior of participants of this study would reach significance.

In several cases, the resulting patterns of response frequencies brought attention to areas of interest. However, these areas require further investigation into the reasoning behind the participants' particular response behavior in order to make accurate evaluations as to how the observed patterns could impact the perceived barriers by female Fabry patients. To accomplish this, a follow up study could include questions that ask participants what symptoms they

consider to be clinically significant and to rate the severity they perceive the symptom to be. For other questions that include scenarios, similar to what was done in this study, survey questions could be designed in a with qualitative methods to ask the participant to provide their reasoning when they answer that they agree in only some cases, compared to when a participant states that they agree for all cases in the provided scenario. Furthermore, targeted questioning that probes the participants' reasoning could obtain insight into any disagreements or misunderstandings the participant may have about their stated utilized clinical practice guidelines, thus providing direction to further investigatory steps towards generating a solution that would result in a higher consistency of clinical practices.

3.4.8 Study Limitations

The purpose of this study was to elicit the practices and beliefs of healthcare providers regarding their care of females with Fabry disease. Survey question content was targeted to specific topics regarding Fabry care. However, the design of this study limited the ability to collect data that fell outside of the targeted categories. Most survey question responses were collected as ordinal data, which by its nature confines the ability to interpret response choices by a true numerical scale. Due to time constraints, the authors were not able to pilot this survey and therefore some questions did not provide an adequate spread of variance to run a statistical analysis. This study was based on a participant population of 58 providers representing three different professional categories and therefore this study did not have a large enough sample size to provide enough statistical power to obtain significance. During recruitment, it is possible that an ascertainment bias may have occurred due to the methods of participant recruitment. Due to the recruitment method via direct contact of selected genetic counselors, participants were recruited in

geographical clusters based on acquaintance to the initially contacted genetic counselors thus potentially limiting the distribution in the geographical representation of participants. This study was based on a population of genetic healthcare providers and therefore the findings should be generally transferrable to genetic healthcare providers overall but should not be generalized to healthcare providers of other fields despite their involvement in the care of patients with Fabry disease. The study population included individuals from several fields of medical genetics but may over or underrepresent some geographical areas.

3.5 CONCLUSIONS

The clinical practices and beliefs of healthcare providers regarding the clinical evaluation, monitoring, and treatment of Fabry disease are not homogeneous among genetics healthcare providers and may evolve at the individual level over time as a provider gains years of experience within the field. In general, views of importance held for each topic of Fabry-related care are more likely to be increased among providers with higher levels of experience compared to those who have less experience. From the results of this study, it appears that the vast majority of providers have an understanding of the complexity of Fabry disease care in a female patient given that not a single response was recorded in this study for “Not important at all” in questions regarding the perception of importance placed on clinical evaluation and monitoring. However, when it comes to the highest levels importance viewed for any given topic, those with more experience were the group most likely to hold this viewpoint.

In general, there was agreement among participants of this study in regards to the responses of the survey, however an increased level of disagreement among providers was noted

in a few key areas. Specifically, these areas were the level of importance placed on the evaluation of a reportedly asymptomatic woman with a 25% risk to have inherited Fabry disease, the interval of clinical evaluations for a symptomatic female patient, and generalized fatigue and malaise as a sole indication for initiating ERT. What these three topics have in common and what sets them apart from the other questions in the survey, is the heightened level of clinical variability, and in turn, unpredictability of disease presentation in a female patient. Applying what has been learned from this study, it is likely that where greater levels of unpredictability exists, providers with higher levels of experience are able to draw from their experience accumulated from their years of practice when making judgements in the clinical decision making process and therefore will be more likely to place higher levels of importance on these complex topics. In order to assist in minimizing the effect of the wide range of clinical practices between less experienced providers and their more experience counterparts on the barriers perceived by female Fabry patients, genetic counselors can utilize their professional skill-sets and training to target these issues during their counseling sessions with female patients. Genetic counselors are well-suited to identify and address the psychosocial impacts on patients created by external or environmental factors. Ultimately, this may assist in improving healthcare outcomes for female patients with Fabry disease.

4.0 RESEARCH SIGNIFICANCE TO GENETIC COUNSELING AND PUBLIC HEALTH

The primary goal of this project was to assess the clinical practices and beliefs of healthcare providers involved in the care of females who are either diagnosed or at-risk for Fabry disease, however, the implications of the project's results are not restricted to this small group of providers alone. In fact, the broader implications of exploring the relationship between provider practices and the health beliefs of their female patients touch upon the importance of both genetic counseling and areas among the core functions of public health as a part of improving the patient healthcare experience. The core functions of public health interact with each other and are collectively vital to the overall working of public health as a system, one that is designed to result in desired outcomes to improve the overall health of the general population. The ten essential functions of public health fall under three core services in the Essential Public Health Services framework: assessment, policy development, and assurance. This project, in its endeavor to improve the patient healthcare experience, involved elements that fit under at least two out of three of these core services in that it investigated the potential involvement of provider practices in the health-beliefs of their female patients (assessment) and the research is being conducted in order to eliminate barriers to access to care (assurance), thus exemplifying the significance to public health and the essential role that genetic counselors can play in the process.

This project was designed to be exploratory in nature, or restated, it was designed to assess the potential of a contribution by providers to the health beliefs of females with Fabry disease through investigating the providers' clinical practices and beliefs. In doing so, this project made the attempt to diagnose and investigate one aspect of the health problem, which is lack of engagement in clinical evaluation, monitoring, and treatment among women with Fabry disease. Even though no hypothesis was formulated and tested in this study, the investigation did reveal results that hold potential to generate further understanding of the elements of the problem. Key areas among provider practices were identified that are speculated to contain higher levels of uncertainty which in turn may cause a wider variability in viewed levels of importance to the health management of female patients by providers with more years of experience. By identifying this element of clinical practice and beliefs of healthcare providers, a clearer picture of the potential contributions to the health beliefs of female patients comes into view, paving the way for interventions to be designed and implemented in the future.

A goal of this three part project was to characterize the health beliefs of females who have been diagnosed or who are at-risk for Fabry disease, so that an improved level of understanding these beliefs can be obtained and strategies can be developed to improve the health outcomes of this population. In other words, this project contributes to the efforts to assure adequate healthcare for this population by attempting to eliminate barriers to access to healthcare. Barriers to Fabry-related clinical care have been identified through investigating the health beliefs of heterozygous females, which was accomplished in parts one and two of the overall project through in-depth interviews and a clinical survey utilized by participating patients. This study, or part three of the overall project, used the themes identified in the previous parts to evaluate a new source of potential influence on the health beliefs of female patients.

Together, the three parts of this project have contributed to a greater understanding of the existing barriers to participating in clinical evaluation, monitoring, and treatment by female Fabry patients, thus paving the way for the design of interventions that will reduce these barriers.

In the clinic, genetic counselors can play a vital role in reducing patients' existing barriers to participating in Fabry-related healthcare. Genetic counselors have specific training and knowledge of how external factors may influence a patient's clinical decision making and behaviors. Therefore, genetic counseling is a suitable, pre-existing service that can be utilized to specifically target the known contributions of barriers related to Fabry disease care in a patient's life. When barriers that are relevant to a patient are identified through open discussion between the patient and the genetic counselor, genetic counselors can proceed to formally counsel the patient on their personal perceptions and coping behaviors to the psychosocial impacts created by the barriers related to Fabry disease, work with the patient to develop personalized strategies aimed at reducing the impact of these barriers, and ultimately improve the patient's healthcare outcomes. This intervention is not a novel model of the practice of genetic counseling, but it does exemplify the critical importance of genetic counseling in the complete delivery of healthcare to the patient.

5.0 SIGNIFICANCE TO PUBLIC HEALTH

Healthcare can only be effective in preventing or lessening the effects of a disease in those who utilize it. Female heterozygotes harboring a mutation in the galactosidase alpha (*GLA*) gene are at risk for developing significant clinical manifestations of Fabry disease but even so, their utilization of clinical evaluations, monitoring, and treatment is often below the optimal frequency for what is necessary to avoid negative health outcomes. As knowledge of the psychosocial issues experienced by female heterozygotes continues to gain recognition as a strong determinant for lack of adherence to recommended care, efforts should be made to integrate this knowledge into a wider clinical practice.

In order to address the problem of barriers and their negative impact on health outcomes, this chapter aims to propose the use of a questionnaire to be utilized by healthcare providers in the clinical setting as a means to initiate a dialogue between the patient and the provider about the patient's potential worries, perceived susceptibility to disease manifestations, and perceived benefits and barriers to evaluation, treatment, and monitoring. Such a questionnaire can be designed to investigate what symptoms, if any, a patient may perceive as "possible to develop" and what symptoms, if any, a patient may perceive as "likely to develop" for both women with Fabry disease in general and for the patient's feelings about herself. By identifying and addressing the psychosocial issues experienced by female heterozygotes, the questionnaire aims

to reduce potential barriers to disease evaluation, monitoring, and treatment and in turn improve disease outcomes and the overall health of women affected by Fabry disease.

Expanding this questionnaire into the broader setting of public health practice by applying its use to women affected by other X linked conditions is a strategy that can be used to facilitate the communication of perceived barriers between patients and their providers and also to emphasize prevention of negative disease outcomes. Even though most X linked conditions do not result in serious manifestations of symptoms in female heterozygotes, the growing list of X linked conditions that are known to clinically affect heterozygous females include, but are not limited to, adrenoleukodystrophy, hemophilia A and B, and ornithine transcarbamylase (OTC) deficiency, along with the rare cases of females affected by skewed X inactivation, warrants a targeted public health intervention.

Such a questionnaire serves as an appropriate population based intervention to reduce perceived barriers to healthcare experienced by women affected by X linked conditions primarily because X linked conditions collectively impact a significant population and knowledge deficiencies regarding the susceptibility of heterozygous females are prevalent. Furthermore, state and local governments have an incentive to reduce the adverse health outcomes of unchecked disease progression due to the healthcare cost of treating the significant negative health outcomes resulting from an X linked genetic disease. For example, a 2006 assessment of the cost effectiveness of ERT in Fabry disease based out of the UK concluded that even though the estimated annual cost of ERT per patient is staggeringly high, within the range of £252,000 to £600,000 (or approximately $312,500 to $744,000) per year, the disease's orphan status, lack of alternative treatment, and reduction in patient life years lost with ERT justify the initiation of treatment in affected individuals.[61]

5.1 EXTENDED APPLICATION TO OTHER X LINKED DISEASES

Similar to Fabry disease, several other X linked disorders have been added to a growing list of X linked conditions that have been recognized as being penetrant in heterozygous females. An exploratory study in 2004 done by Dobyns et al. analyzed 36 different X linked disorders for their disease severity and penetrance in both male and female populations, finding that both severity and penetrance were always equal to or higher in males than in females. However, in likeness to Fabry disease, many of the conditions were also found to have wider variabilities in both severity and penetrance in females.[38] Furthermore, because these X linked conditions share similar disparities to Fabry disease in severity and penetrance between males and females, it is possible that they share a similar susceptibility to a devalued carrier status.

The range of severity of manifestations in females heterozygous for Fabry disease was underappreciated until recently because of the misconception that the X linked inheritance of Fabry disease protected females from manifestations and, in most cases, females' physical disease burden was not as severe, nor as recognizable as it was in males. Unfortunately, these issues may not be specific to Fabry disease and may occur in other X linked conditions as well. Additionally, female heterozygotes of other X linked conditions could be susceptible to their own unique set of psychosocial burdens, comparable to the burdens experienced by females in Fabry disease. Overall, there are a number of X linked conditions that closely resemble the Fabry disease model of female heterozygote burden, warranting further application of the health belief questionnaire beyond Fabry disease. The following sections of this chapter explore three examples of X linked conditions in which the lives of female heterozygotes affected by the condition have potential to be improved through the use of the clinical questionnaire.

5.1.1 Fragile X Syndrome

Well characterized in males, Fragile X syndrome is one of the most common genetic causes of intellectual disability and autism spectrum disorder (ASD).[62] Manifestations arise through an X linked repeat expansion of CGG trinucleotides in the 5' untranslated region of the *FMR1* gene, located on the X chromosome. A normal allele is characterized by a length of 6-54 repeats, a premutation is characterized by 55-200 repeats, and repeats of ≥200 trinucleotides result in a full mutation.[63] The classic manifestations of Fragile X affect males who harbor a full mutation for the condition with a characteristic phenotype, most prominent after puberty, and a spectrum of developmental and behavioral issues, seizures, and moderate to severe intellectual disability. In females heterozygous for the full mutation, a milder and more variable presentation is possible, typically with a normal intellectual functioning or borderline intellectual disability, learning disabilities, and social dysfunction.[64] Other manifestations in females can take place when a woman harbors an allele in the premutation range, but again, presentation and severity are highly variable. In the premutation range, female heterozygotes are at an increased risk of Fragile X-associated premature ovarian failure (FXPOF) causing them to undergo menopause usually before the age of 40, and a neurodegenerative disorder called Fragile X-associated tremor/ataxia syndrome (FXTAS) resulting in action tremors and gait ataxia developing after the age of 50.[65,66]

Several unique psychosocial impacts stemming from the diagnosis of Fragile X, FXPOF, and FXTAS are presumed to exist despite the limited data on the subject. For premature ovarian failure, evidence can be gleaned from extrapolating findings from other studies not specific to Fragile X. Notably, a cross-sectional study examining 77 women with premature ovarian failure of several etiologies found that compared to controls, these women had significantly higher occurrences of depression, anxiety, body image, sexual dysfunction, and self-confidence.[67] In

women whose lives were affected by FXTAS, a study designed to assess the needs of patients and their caregivers found that informational resources were ranked by study participants as the most important need for themselves, followed by emotional, and then instrumental needs. The authors acknowledged difficulties in delivering the informational needs, citing the evolving clinical picture of FXTAS, geographic barriers to research studies, and a paucity of providers familiar with FXTAS.[68]

5.1.2 Ornithine Transcarbamylase (OTC) Deficiency

Females may only rarely be affected by the neo-natal onset form of Ornithine Transcarbamylase Deficiency (OTC) but they are much more commonly affected by the post-neo-natal onset (partial) form of OTC deficiency which can manifest at any time from infancy to well into adulthood.[69,70] OTC deficiency is an X linked disorder caused by a lack of ornithine transcarbamylase enzyme which is needed to clear the body of excess nitrogen in the urea cycle. Without this enzyme, excess ammonia accumulates in the bloodstream, damaging the central nervous system and the brain and resulting in vomiting, lethargy, and coma.[71] Symptoms of later-onset OTC deficiency typically manifest after making dietary changes from breast milk to formula or whole milk during infancy or from undergoing significant stressors including febrile illness, high-protein diets, post-operatively, or during the post-partum period.[72–74] At a minimum, it has been estimated that at least 15% of heterozygous females express some level of symptoms, however it is predicted that the true percentage of affected heterozygous females is much higher, hidden by a lack of a medical diagnosis.[69] For many heterozygous women, a diagnosis only occurs via methods of cascade screening after a more severely affected relative is identified.

There is a paucity of literature exploring the effects of a diagnosis of OTC deficiency on a heterozygous female's psychosocial adaptation and functioning. Nevertheless, the course of OTC deficiency manifestations in female heterozygotes shares similar traits with the course of Fabry disease diagnosis in heterozygous females, and therefore concepts can be extrapolated. Fabry disease heterozygotes, and likely OTC deficiency heterozygotes, have been commonly found to deny the presence of any personal risk to develop clinical manifestations of the disease and have been identified as more likely to attend clinical evaluations in accompaniment of their affected sons or male relatives, rather than attend for the benefit of their own health evaluation.[2,5] This behavior is thought to be the product of perceived barriers to engaging in Fabry-related care due to the uncommonness of Fabry disease, the prevailing misconception that female heterozygotes are unaffected carriers of the disease or only express mild symptoms, and the disparity between healthcare treatment of men and women.[11]

5.1.3 Hemophilia A

Factor VIII clotting deficiency, also known as Hemophilia A or classical Hemophilia, is an X linked disorder which manifests in prolonged episodes of bleeding, and in more severe cases, episodes of spontaneous internal bleeding. Among affected individuals, the disorder can widely range in clinical severity. Individuals with less than 40% functional factor VIII protein will be affected with at-least some clotting deficiency. This holds true for heterozygous females as well, where about 30% of heterozygous females have functioning factor VIII levels of 40% or lower, making them susceptible to develop clinical manifestations to a degree that is akin to their male counterparts. Additionally, heterozygous females have also been reported to express milder forms of the condition at factor VIII levels between 35 to 60%.[75,76]

Multiple studies analyzing the psychosocial impact of Hemophilia A on female heterozygotes have found that women with the disease generally experience a variety of psychosocial burdens including a reduced quality of life compared to their healthy counterparts, reduced employment or restrictions in job performance, and stigmatization as a result of their disease.[77–79] Additionally, the disease has been identified as influencing the mental health of female heterozygotes in terms of life satisfaction, self-esteem, anxiety, and depression.[80–83] Each of these areas of burden are amenable to targeted intervention as a means to optimize clinical health outcomes and improve quality of life among affected patients. Furthermore, a Finnish study investigating the impact of diagnoses made in adolescence found that 22% of mothers failed to correctly recall their daughters' genetic testing results and that the majority of these children did not follow up with receiving genetic counseling once they reached adulthood, thus placing themselves at a disadvantage for managing their potential disease manifestations in the future.[84]

5.2 PROPOSED INTERVENTION

Parts one and two of this three part study identified a decreased perception of personal susceptibility to clinical manifestations of Fabry disease in heterozygous female study participants, even though the corresponding knowledge base regarding the clinical course of Fabry disease was identified to be largely accurate. Views of decreased personal susceptibility, and influencers of decision making in regards to engaging in clinical evaluation, monitoring, and treatment, were primarily identified by the study participants as stemming from feelings of denial, grief, guilt, excessive worry, sadness, anxiety, and feelings of being overwhelmed.

Furthermore, in part three of the study, participating healthcare providers noted a lack of compliance to clinical evaluation, monitoring, and treatment in the female heterozygotes involved in their care. Overall, each part of the study highlights existing psychosocial barriers to engaging in preventative health behaviors for heterozygous females affected by Fabry disease likely contributing to the occurrence of preventable disease outcomes. With the utilization of a questionnaire by healthcare providers as a means of enabling discussion between the provider and the patient, barriers to engaging in preventative health behaviors for patients can be targeted and addressed in not only patients heterozygous for Fabry disease, but for patients of other X linked disorders as well. This proposed intervention aims to facilitate communications between the patient and the provider about perceived barriers to clinical evaluation, monitoring, and treatment as a means to improve patient compliance with recommended therapies and optimize clinical outcomes.

A questionnaire serves as a suitable tool for this particular need because it can be administered outside of the clinical session to avoid infringement on the already limited amount of time that is available for the provider to meet with a patient during a clinical session. The questionnaire has advantages over other forms of information collection in that it can be administered and completed ahead of the appointment for the provider to review prior to the beginning of the session, either electronically, or as a form that can be mailed to the patient for completion, or as a form given to the patient to complete in the waiting room directly before the appointment. Acknowledgement and respect for the time constraints that individual providers may have available to review any additional information about their patients is essential for the success of the intervention, and therefore it is critical that this questionnaire collects information in a concise and effective way. The goal of the questionnaire as an intervention would be to

screen for individuals who display signs of being susceptible to barriers to participating in routine disease monitoring or treatment, so that the providers can be notified of important issues to address during a session prior to the appointment with the patient.

Similar interventions with various modes of implementation have been successfully utilized in screening for mental health issues in the primary care setting. A 2013 study evaluating the utility of mental health screening administered by mail in a pediatric population in the context of primary care concluded that screening for mental health can be performed effectively in primary care practice.[85] Screening for mental health issues via web-based methods in the primary care pediatric population has also received evidence supporting its effectiveness, as was determined by a study performed in 2013, which noted a particular advantage to the tool being that it assisted providers in balancing psychosocial and somatic concerns during routine appointments.[86] Furthermore, a 2015 study utilizing an interactive voice response (IVR) system by phone to administer screening for lifestyle and behavioral risk factors in adults in the primary care setting identified that the IVR tool compared well to other screening methods in terms of the screened-for behaviors and was concluded to be an effective tool for screening in the primary care clinic.[87] Each of these studies exemplify the benefits and utility of a questionnaire screening tool that can be utilized in the primary care setting in multiple forms, thus displaying potential for such a tool to be adapted to screening for patients who are susceptible to barriers to participating in their own X linked disease-related care.

For any X linked disease of interest that is known to affect the health of female heterozygotes to some degree, the proposed questionnaire can be employed by providers as a tool to elicit a heterozygous female patient's knowledge, perceived susceptibility, and attitudes towards the disease and any corresponding treatment. By acknowledging the patient's

perspective, this strategy can be utilized to diminish conflict regarding adherence to provider clinical recommendations and ultimately improve disease outcomes. Specifically, the questionnaire will include topics such as:

1. Assessing the patient's knowledge of potential symptoms of X linked disease of interest in both males and females
2. Assessing levels of patient acknowledgement of their own symptoms (if present) and the patient's beliefs regarding the potential to develop symptoms in the future
3. Assessing the patient's perception of the severity of the disease of interest in both males and females
4. Assessing the patient's knowledge regarding the inheritance pattern of the disease of interest
5. Assessing the patient's status of diagnosis for the disease of interest and feelings associated with the receipt of a diagnosis
6. Assessing the patient's level of fear or worry regarding the disease of interest
7. Assessing the presence of factors that are established as having potential to exacerbate barriers to clinical monitoring and treatment (i.e. time, finances, feelings of anxiety or depression)
8. Assessing the level of compliance with clinical recommendations for disease monitoring and treatment

After the questionnaire has been completed by the patient, the administering provider can then use the patient's responses to engage in a discussion with the patient regarding any identified issues. In doing so, the provider can provide educational, empathetic, and psychosocial support to the patient which might not have otherwise been initiated.

For example, a patient who demonstrates a misconception of the degree of her susceptibility to the genetic condition may require further education about the penetrance and severity of certain manifestations in females. Successfully educating the patient about her risks to the disease has the potential to increase the likelihood that she will follow recommended disease monitoring and treatment. A patient who demonstrates strong feelings of fear or anxiety about the disease may require increased explicit verbalization of empathetic support and guidance from the provider team, or in some cases may benefit from the referral to a mental health specialist, in order to decrease and quell these feelings in the patient. As previously discussed in patients diagnosed with Fabry disease, patients experiencing higher levels of anxiety, fear, and stress regarding disease monitoring and treatment are less likely to comply with recommended monitoring and treatment. A patient who cites a lack of resources, such as transportation or finances, may necessitate connection with the institution's social worker for assistance in accessing these resources. In each of these scenarios, targeted discussion of the identified issues between the patient and the provider takes a step towards the goal of improving the patient's engagement in preventative health behaviors. When applied broadly to a large population of individuals susceptible to these barriers, an improvement of disease outcomes at the population level may be achieved.

5.3 INTERVENTION EVALUATIONS

In order to determine the effectiveness of the questionnaire in reducing the incidence of X linked disease-associated negative health outcomes in heterozygous females prior to investing in the large cost of wide-scale implementation, a small-scale pilot project is needed. In this project,

initial implementation and short-term evaluation of the effectiveness of the questionnaire as a public health intervention will take place among primary care providers (PCPs) in Pittsburgh, PA and then, pending promising results, will be extended to PCP clinics across the state of Pennsylvania for long-term assessment within a larger population. To organize the smooth implementation of the questionnaire among participating clinics, the pilot program coordinator for this evaluation will be tasked with recruiting PCPs, educating them on the use of the questionnaire, and distributing the materials to participating sites. To indirectly measure the effectiveness of the questionnaire in reducing the incidence of disease-related negative health outcomes, anonymous data regarding patient compliance to recommended clinical monitoring, knowledge about their disease, and negative feelings surrounding their diagnosis, prognosis, or care will be collected from the participating PCPs via an evaluation survey at several different time points, developed by the pilot-study coordinators. Responses collected from the data gathering survey will be used to assess the impact of the intervention over time from the initiation of the pilot program. The logic follows that increased patient involvement in routine evaluation, monitoring, and treatment (as needed) for their disease would result in reduced negative disease outcomes in the long-term. Therefore, improved patient compliance, disease knowledge, and feelings surrounding the diagnosis should suffice as surrogate evidence of the effectiveness of the questionnaire.

In total, the pilot study will undergo 4 to 5 years of data collection and evaluation in the state of Pennsylvania before the questionnaire can be validated for use as a nationwide public health measure. In the manner previously described, in the first two years of the study the implementation of the questionnaire will be confined to the smaller region and population of Pittsburgh, PA in order to minimize the expense of the pilot program while obtaining preliminary

data that would confirm or refute the effectiveness of the questionnaire. Time points for data collection via survey will take place at baseline (defined as the time of implementation of the use of the questionnaire at a particular participating clinic) and then in six month intervals. If the results from the first two years of the pilot study indicate a favorable direction in improved patient compliance to recommended evaluations, monitoring, and treatment, then the study can be expanded to the larger population and region of the entirety of the state of Pennsylvania to confirm applicability of the findings to other geographic areas. However, due to the logistics entailing the implementation of the questionnaire to such a large region, the second half of this pilot program will require a longer period of time to allow for adequate PCP participant recruitment and education regarding their role in the pilot study. Nevertheless, the implementation and data collection will follow the same outline as the first part of this program.

Effectiveness of the pilot program will be measured in the short-term by assessing participating PCPs' report of their patients' behavior in regards to engaging in recommended clinical monitoring and treatment for their disease. The survey used to elicit this information from the participating PCPs will include free text fields where providers can include anecdotal feedback regarding the conversations that took place with their patients after implantation of the questionnaire. Any feedback received can be utilized for making improvements to the program and adjusting to the previously unforeseen needs of participating providers and their patients. Other variables used to measure the impact of the program, such as clinical outcomes, will require longer durations of time for adequate assessment and thus will be included in the long-term assessments of the pilot program, likely after the intervention has been implemented nation-wide.

5.4 CONCLUSIONS

The intent of this intervention is to reduce negative health outcomes in female heterozygous patients affected by an X linked condition through identifying and addressing barriers to participating in clinical evaluation, monitoring, and treatment. Individually, X linked conditions affect only a fraction of the general population, however, collectively X linked conditions affect a population that is large enough to warrant a wide spread intervention. Identifying and addressing barriers can be achieved through the use of a clinical questionnaire, enabling medical providers to screen for patients who are susceptible to barriers to participating in clinical care. Once a patient has been identified by the questionnaire, the provider can address the issues reported by the patient and work with the patient to develop strategies to reduce these barriers during a clinical session, and thereby ultimately prevent negative health outcomes in the patient's future.

In order to test and evaluate the effectiveness of the proposed intervention, it is necessary for a small pilot study to be conducted. To conserve expenditure on the intervention in the initial stages of the evaluation, the questionnaire will be tested for its effectiveness with a small sample of participants consisting of primary care providers in the city of Pittsburgh, PA before being expanded to a larger sample of PCPs across the entire state of Pennsylvania. Data collection will take place in six month intervals via a short survey to participating providers to assess the effectiveness of the questionnaire over the time period of the pilot project. The survey will collect both short-term and long-term data to be used to determine the effectiveness of the questionnaire by eliciting the PCPs' report of their patients' behavioral patterns in regards to clinical monitoring and treatment for their X linked condition, and by collecting clinical outcomes of patients seen by participating PCPs. Given that the data collected in the small-scale

part of the project displays promising results about the effectiveness of the questionnaire, the project will then be allowed to be instituted for use in the larger population of the state of Pennsylvania, and then nationwide, to improve the lives of female heterozygous patients across the country.

APPENDIX A: IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: David Finegold

From: IRB Office

Date: 12/16/2016

IRB#: PRO16080196

Subject: ASSESSING CLINICAL PRACTICES AND BELIEFS AMONG PROVIDERS FOLLOWING WOMEN DIAGNOSED OR AT-RISK FOR FABRY DISEASE

The above-referenced project has been reviewed by the Institutional Review Board. Based on the information provided, this project meets all the necessary criteria for an exemption, and is hereby designated as "exempt" under section

45 CFR 46.101(b)(2)

Please note the following information:

- Investigators should consult with the IRB whenever questions arise about whether planned changes to an exempt study might alter the exempt status. Use the "**Send Comments to IRB Staff**" link displayed on study workspace to request a review to ensure it continues to meet the exempt category.
- It is important to close your study when finished by using the "**Study Completed**" link displayed on the study workspace.
- Exempt studies will be archived after 3 years unless you choose to extend the study. If your study is archived, you can continue conducting research activities as the IRB has made the determination that your project met one of the required exempt categories. The only caveat is that no changes can be made to the application. If a change is needed, you will need to submit a NEW Exempt application.

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B: PARTICIPANT RECRUITMENT EMAIL INVITATION

Email Script for Healthcare professional recruitment:

Subject: Assessing clinical practices and beliefs among providers following women diagnosed or at-risk for Fabry disease

Dear Healthcare Professional,

You are invited to participate in a research study. The purpose of this study is to **better understand the health beliefs of women diagnosed and at-risk for Fabry disease.** In order to assess how these health beliefs might be influenced, we will be surveying healthcare professionals involved in the care of women diagnosed and at-risk for Fabry disease. All individuals involved in the evaluation, monitoring, and/or treatment of individuals with Fabry disease are invited to participate. This study is being conducted by Bryony Lynch, a second year student at the University of Pittsburgh Genetic Counseling Program.

Your participation would include completing this 10-15 minute online survey. This survey will assess your clinical practices and beliefs about the importance of clinical care for women with Fabry disease and your use of published medical management recommendations. This is an entirely anonymous survey, and so your responses will not be identifiable in any way. All responses are confidential, and results will be kept under a password protected computer. Your participation is voluntary. By completing this survey, you are agreeing to participate in this study. You may withdraw from the study at any time before submitting your survey responses.

There are no foreseeable risks associated with this project, nor are there any direct benefits to you. Participants will not receive any payment for participation.

To complete this survey, please use the following link (you may have to copy and paste the entire link into your browser):

[*Insert internet link to Qualtrics here*]

If you would like to contact the study team for any comments or questions, please email Bryony Lynch or Nadene Henderson via the contact information below.

Thank you for your time and consideration.

Sincerely,

Bryony Lynch
Genetic Counseling Student
University of Pittsburgh
Bml53@pitt.edu

Nadene Henderson MS, LCGC
Genetic Counselor
Children's Hospital of Pittsburgh
Nadene.Henderson@chp.edu

Follow-up Email Script for Healthcare professional recruitment:

The follow-up email script will contain the exact wording as stated in the original email script. However, the subject headline of the email will contain "Reminder: Assessing clinical practices and beliefs among providers following women diagnosed or at-risk for Fabry disease"

APPENDIX C: PARTICIPANT SURVEY

A Survey of Providers Caring for Females with Fabry Disease

Intro: We thank you for participating in this survey. This survey is part of a research study to examine the health beliefs of females diagnosed or at risk for Fabry disease. Your responses will be used in the analysis of data gathered on the knowledge and current practices of healthcare providers involved in the care of adult women with Fabry disease. For the purposes of this survey, the term "adult" refers to a person over the age of 18 years. If there is a question that you do not feel comfortable answering, you can skip it and continue on. Please answer the following questions to the best of your ability. The survey should take approximately 10-15 minutes. We would like to thank you in advance for your willingness to participate in this study.

Q1 Are you a professional who participates in the evaluation, management, and/or treatment of adult females diagnosed or at risk for Fabry disease?

- ❍ Yes (1)
- ❍ No (2)
- ❍ Don't know/Not sure (3)

If Don't know/Not sure Is Selected, Then Skip To End of Survey. If No Is Selected, Then Skip To End of Survey

Q2 Please identify your current position

- ❍ Physician (1)
- ❍ Physician Assistant (2)
- ❍ Nurse (3)
- ❍ Nurse Practitioner (4)
- ❍ Genetic Counselor (5)
- ❍ Other (6) _____

If Genetic Counselor Is Selected, Then Skip To End of Block. If Nurse Is Selected, Then Skip To End of Block

Q3 Please identify your specialty

Q4 Collectively, how many years have you participated in the evaluation, management, and/or treatment of adults with Fabry disease?

- ❍ Less than one year (1)
- ❍ One year up to five years (2)
- ❍ Five years up to ten years (3)
- ❍ Ten years or greater (4)

Q5 How long have you been working with adults with Fabry disease at your current institution?

- ❍ Less than one year (1)
- ❍ One year up to five years (2)
- ❍ Five years up to ten years (3)
- ❍ Ten years or greater (4)

Q6 How many adult females diagnosed with Fabry disease does your clinical practice currently follow?

- ❍ Less than 5 (1)
- ❍ Between 5-10 (2)
- ❍ Between 11-20 (3)
- ❍ 21 or more (4)

Q7 How many adult females diagnosed with Fabry disease do you follow clinically?

- ❍ Less than 5 (1)
- ❍ Between 5-10 (2)
- ❍ Between 11-20 (3)
- ❍ 21 or more (4)

Q8 Clinicians often choose to treat their patients in different ways. The following questions will give you an opportunity to tell us about your own clinical practice.

Q9 Please identify the level of importance you place on an initial clinical genetics evaluation for an adult woman in the following scenarios:A) A reportedly asymptomatic woman with a family history indicating she has inherited Fabry disease (Example: Affected father)

- ❍ Very important (1)
- ❍ Important (2)
- ❍ Somewhat important (3)
- ❍ Not important at all (4)
- ❍ Don't know / Not sure (5)

Q10 B) A reported asymptomatic woman with a family history indicating she is at 50% risk to have inherited Fabry disease (Example: Affected brother)

- ❍ Very important (1)
- ❍ Important (2)
- ❍ Somewhat important (3)
- ❍ Not important at all (4)
- ❍ Don't know / Not sure (5)

Q11 C) A reportedly asymptomatic woman with a family history indicating she is at 25% risk to have inherited Fabry disease (Example: Affected maternal uncle)

- ❍ Very important (1)
- ❍ Important (2)
- ❍ Somewhat important (3)
- ❍ Not important at all (4)
- ❍ Don't know / Not sure (5)

Q12 D) A woman with a reported history of myocardial infarction and a family history indicating she is at 50% risk to have inherited Fabry disease (Example: Affected brother)

- ❍ Very important (1)
- ❍ Important (2)
- ❍ Somewhat important (3)
- ❍ Not important at all (4)
- ❍ Don't know / Not sure (5)

Q13 E) A woman with a reported history of myocardial infarction and a family history indicating she is at 25% risk to have inherited Fabry disease (Example: Affected maternal uncle)

- ❍ Very important (1)
- ❍ Important (2)
- ❍ Somewhat important (3)
- ❍ Not important at all (4)
- ❍ Don't know / Not sure (5)

Q14 F) A woman with a reported history of left ventricular hypertrophy and burning pain in her hands and feet with no known family history of Fabry disease

- ❍ Very important (1)
- ❍ Important (2)
- ❍ Somewhat important (3)
- ❍ Not important all (4)
- ❍ Don't know / Not sure (5)

Q15 What term(s) do you use to describe an adult female who has inherited a mutation in the Fabry gene but does not have symptoms of Fabry disease? (Please select all that apply.)

- ❑ Carrier (1)
- ❑ Fabry female (2)
- ❑ Female heterozygote (3)
- ❑ Asymptomatic female (4)
- ❑ Other (5) _____

Q16 What term(s) do you use to describe an adult female who has inherited a mutation in the Fabry gene and has symptoms of Fabry disease? (Please select all that apply.)

- ❑ Carrier (1)
- ❑ Fabry female (2)
- ❑ Female heterozygote (3)
- ❑ Symptomatic female (4)
- ❑ Other (5) _____

Q17 To your knowledge, after full genetic, cardiac, renal, and neurologic evaluations, an asymptomatic adult female with confirmed Fabry disease should be recommended to be evaluated by a physician knowledgeable in Fabry disease every...

- ❍ Three months (1)
- ❍ Six months (2)
- ❍ Twelve months (3)
- ❍ Eighteen months (4)
- ❍ Two years (5)
- ❍ Other (6) _____

Q18 To your knowledge, a symptomatic adult female with confirmed Fabry disease should be recommended to be evaluated with a physician knowledgeable in Fabry disease every...

- ❍ Three months (1)
- ❍ Six months (2)
- ❍ Twelve months (3)
- ❍ Eighteen months (4)
- ❍ Two years (5)
- ❍ Other (6) _____

Q19 Do you refer to any specific protocols or guidelines when recommending clinical monitoring and frequency for an adult male diagnosed with Fabry disease?

- ❍ Yes (1)
- ❍ No (2)
- ❍ Don't know / Not sure (3)
- ❍ I am not involved in the decision to recommend clinical monitoring (4)

If No Is Selected, Then Skip To End of Block. If I am not involved in the de... Is Selected, Then Skip To End of Block

Q20 Please indicate which of the following protocols or guidelines you refer to when recommending clinical monitoring and frequency for an adult male diagnosed with Fabry disease? (Please select all that apply.)

- ❑ Center protocol (1)
- ❑ Published literature / Document (2)
- ❑ Industry produced assessment guidelines (3)
- ❑ Other protocols or guidelines (4)
- ❑ Personal experience (5)
- ❑ Don't know / Not sure (6)

If Center protocol Is Selected, Then Skip To End of Block. If Personal experience Is Selected, Then Skip To End of Block. If Don't know / Not sure Is Selected, Then Skip To End of Block. If Please indicate which of th... Is Equal to 0, Then Skip To End of Block

Q21 Please specify the ‘other protocols or guidelines’

Q22 Do you refer to any specific protocols or guidelines when recommending clinical monitoring and frequency for an adult female diagnosed with Fabry disease?

- ❍ Yes (1)
- ❍ No (2)
- ❍ Don't know / Not sure (3)
- ❍ I am not involved in the decision to recommend clinical monitoring (4)

If No Is Selected, Then Skip To End of Block. If I am not involved in the de... Is Selected, Then Skip To End of Block

Q23 Please indicate which of the following protocols or guidelines you refer to when recommending clinical monitoring and frequency for an adult female diagnosed with Fabry disease? (Please select all that apply.)

- ❑ Center protocol (1)
- ❑ Published literature / Document (2)
- ❑ Industry produced assessment guidelines (3)
- ❑ Other protocols or guidelines (4)
- ❑ Personal experience (5)
- ❑ Don't know / Not sure (6)

If Center protocol Is Selected, Then Skip To How beneficial do you think the proto...If Personal experience Is Selected, Then Skip To How beneficial do you think the proto...If Don't know / Not sure Is Selected, Then Skip To How beneficial do you think the proto...If Please indicate which of th... Is Equal to 0, Then Skip To End of Block

Q24 Please specify the ‘other protocols or guidelines’

Q25 How beneficial do you think the protocol or guidelines used by you (as mentioned previously) are to formulating clinical monitoring recommendations for an adult female with Fabry disease?

- ❍ Very beneficial (1)
- ❍ Beneficial (2)
- ❍ Somewhat beneficial (3)
- ❍ Don't know / Not sure (4)

Q26 In your opinion, how important do you believe frequent clinical monitoring (e.g. urine protein excretion every 6 months, echocardiogram annually, brain MRI every 2-3 years, etc) is to the overall management of an adult female with Fabry disease?

- ❍ Very important (1)
- ❍ Important (2)
- ❍ Somewhat important (3)
- ❍ Not important at all (4)
- ❍ Don't know / Not sure (5)

Q27 Do you believe adult females with Fabry disease should be clinically monitored as frequently as adult males with Fabry disease?

- ❍ Yes, in all cases (1)
- ❍ Yes, in some cases (2)
- ❍ No, never (3)
- ❍ Don't know / Not sure (4)

Q28 Enzyme replacement therapy (ERT) is a treatment option which can be utilized to treat symptomatic individuals with Fabry disease. Please answer the next group of questions regarding enzyme replacement therapy in your clinical practice.

Q29 How many adult females diagnosed with Fabry disease does your clinical practice currently treat with enzyme replacement therapy (ERT)?

- ❍ None (1)
- ❍ Less than 5 (2)
- ❍ Between 5-10 (3)
- ❍ Between 11-20 (4)
- ❍ 21 or more (5)
- ❍ Don't know / Not sure (6)

If None Is Selected, Then Skip To End of Block

Q30 Please read the following excerpt, then answer the question based on the excerpt: "Females with Fabry disease should be offered ERT if they manifest significant symptoms or show evidence of progressive end organ Fabry involvement including: chronic acroparesthesias resistant to conventional therapy, persistent proteinuria (>300mg/24hrs), GFR below 80nL/minute/1.73m2, clinically significant cardiac involvement, a previous cerebrovascular accident or history of transient ischemic attacks, or ischemic changes on brain MRI" (Eng et al 2006). Do you follow the guidelines that are listed in the previous excerpt (Eng et al 2006) when deciding to recommend enzyme replacement therapy (ERT) for an adult female with confirmed Fabry disease?

- ❍ Yes, in all cases (1)
- ❍ Yes, in some cases (2)
- ❍ No, never (3)
- ❍ I am not involved in the decision to recommend ERT (4)
- ❍ Don't know / Not sure (5)

If I am not involved in the de... Is Selected, Then Skip To End of Block

Q31 Do you refer to other literature or documents when recommending enzyme replacement therapy (ERT) for an adult female with confirmed Fabry disease?

- ❍ Yes (1)
- ❍ No (2)
- ❍ Don't know / Not sure (3)

If No Is Selected, Then Skip To How helpful are the guidelines cited ...If Don't know / Not sure Is Selected, Then Skip To How helpful are the guidelines cited ...

Q32 Please specify the other literature or documents that you refer to when recommending enzyme replacement therapy (ERT) for an adult female with confirmed Fabry disease.

Display This Question:
If Please read the following excerpt, then answer the question based on the excerpt: "Females with Fabry disease should be offered ERT if they manifest significant symptoms or show evidence of progr... No, never Is Not Selected

Q33 How helpful are the guidelines cited in the previous question (Eng et al 2006) when formulating your clinical decision to recommend enzyme replacement therapy (ERT) for an adult female with Fabry disease?

- Very helpful (1)
- Helpful (2)
- Somewhat helpful (3)
- Not helpful at all (4)
- Don't know / Not sure (5)

Q34 The next set of questions will provide an opportunity for you to convey your opinions regarding your decisions on initiating enzyme replacement therapy (ERT) for patients. Please answer the questions based on your own beliefs.

Q35 Please indicate if you believe chronic, disabling gastrointestinal dysfunction is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult female with Fabry disease.

- Yes, in all cases (1)
- Yes, in some cases (2)
- No, never (3)
- Don't know / Not sure (4)

Q36 Please indicate if you believe pulmonary involvement is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult female with Fabry disease.

- Yes, in all cases (1)
- Yes, in some cases (2)
- No, never (3)

- ❍ Don't know / Not sure (4)

Q37 Please indicate if you believe abnormal blood pressure regulation during exercise testing is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult female with Fabry disease.

- ❍ Yes, in all cases (1)
- ❍ Yes, in some cases (2)
- ❍ No, never (3)
- ❍ Don't know / Not sure (4)

Q38 Please indicate if you believe generalized fatigue and malaise is a potential sole consideration to initiating enzyme replacement therapy (ERT) for an adult female with Fabry disease.

- ❍ Yes, in all cases (1)
- ❍ Yes, in some cases (2)
- ❍ No, never (3)
- ❍ Don't know / Not sure (4)

Q39 Please answer the next group of questions based on your experience with patients.

Q40 How do you characterize the degree of Fabry female patient compliance with recommended clinical evaluations?

- ❍ Highly compliant (1)
- ❍ Moderately compliant (2)
- ❍ Slightly compliant (3)
- ❍ Not at all compliant (4)
- ❍ Don't know / Not sure (5)

Q41 How do you characterize the degree of Fabry female compliance with recommended clinical monitoring (e.g. 24 hour urine for total protein, echocardiogram, brain MRI, etc)?

- ❍ Highly compliant (1)
- ❍ Moderately compliant (2)
- ❍ Slightly compliant (3)
- ❍ Not at all compliant (4)
- ❍ Don't know / Not sure (5)

Q42 When a patient is recommended for enzyme replacement therapy (ERT), how do you characterize the degree of Fabry female compliance with recommended enzyme replacement therapy.

- ❍ Highly compliant (1)
- ❍ Moderately compliant (2)
- ❍ Slightly compliant (3)
- ❍ Not at all compliant (4)
- ❍ Don't know / Not sure (5)

Q43 End of Survey. Thank you again for your participation. If you have any questions regarding this survey, please feel free to contact the head of this study, Nadene Henderson MS, LCGC at Nadene.Henderson@chp.edu or Bryony Lynch Genetic Counseling Student at bml53@pitt.edu

BIBLIOGRAPHY

1. Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic Defect in Fabry's Disease. *N Engl J Med*. 1967;276(21):1163-1167. doi:10.1056/NEJM196705252762101.

2. MacDermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J Med Genet*. 2001;38(11):769-775. doi:10.1136/JMG.38.11.769.

3. Macdermot KD, Holmes A, Miners AH. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J Med Genet*. 2001;38:750-760.

4. Bennett RL, Hart KA, O 'rourke E, et al. Fabry Disease in Genetic Counseling Practice: Recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2002;11(2):121-146.

5. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genet Med*. 2007;9(1):34-45. doi:10.1097/GIM.0b013e31802d8321.

6. Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: Guidelines for the evaluation and management of multi-organ system involvement. *Genet Med*. 2006;8(9):539-584. doi:10.1097/01.gim.0000237866.70357.c6.

7. Watt T, Burlina AP, Cazzorla C, et al. Agalsidase beta treatment is associated with improved quality of life in patients with Fabry disease: Findings from the Fabry Registry. *Genet Med*. 2010;12(11):703-712. doi:10.1097/GIM.0b013e3181f13a4a.

8. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-Beta Therapy for Advanced Fabry Disease A Randomized Trial for the Fabry Disease Clinical Trial Study Group*. *Ann Intern Med*. 2007;146:77-86.

9. Tøndel C, Bostad L, Larsen KK, et al. Agalsidase Benefits Renal Histology in Young Patients with Fabry Disease. *J Am Soc Nephrol*. 2013;24:137-148. doi:10.1681/ASN.2012030316.

10. Ito S, Ogura M, Kamei K, Matsuoka K, Warnock DG. Significant improvement in Fabry disease podocytopathy after 3 years of treatment with agalsidase beta. *Pediatr Nephrol*. 2016;31(8):1369-1373. doi:10.1007/s00467-016-3387-4.

11. Gibas AL, Klatt R, Johnson J, Clarke JTR, Katz J. Disease rarity, carrier status, and gender: A triple disadvantage for women with Fabry disease. *J Genet Couns*. 2008;17:528-537. doi:10.1007/s10897-008-9179-7.

12. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: Baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest*. 2004;34:236-242. doi:10.1111/j.1365-2362.2004.01309.x.

13. Spada M, Pagliardini S, Yasuda M, et al. High Incidence of Later-Onset Fabry Disease Revealed by Newborn Screening. *Am J Hum Genet*. 2006;79:31-40. www.ajhg.org.

14. Lin HY, Chong KW, Hsu JH, et al. High incidence of the cardiac variant of fabry disease revealed by newborn screening in the Taiwan Chinese population. *Circ Cardiovasc Genet*. 2009;2:450-456. doi:10.1161/CIRCGENETICS.109.862920.

15. Hwu W-L, Chien Y-H, Lee N-C, et al. Newborn Screening for Fabry Disease in Taiwan Reveals a High Incidence of the Later-Onset Mutation c.936+919G>A (IVS4+919G>A). *Hum Mutat*. 2009;30(10):1397-1405. doi:10.1002/humu.21074.

16. Mechtler TP, Stary S, Metz TF, et al. Neonatal screening for lysosomal storage disorders: Feasibility and incidence from a nationwide study in Austria. *Lancet*. 2012;379:335-341. doi:10.1016/S0140-6736(11)61266-X.

17. von der Lippe C, Frich JC, Harris A, Solbr????kke KN. Experiences of Being Heterozygous for Fabry Disease: a Qualitative Study. *J Genet Couns*. 2016;25(5):1085-1092. doi:10.1007/s10897-016-9941-1.

18. Chimenti C, Pieroni M, Morgante E, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circ Cardiovasc Genet*. 2004;110:1047-1053. doi:10.1161/01.CIR.0000139847.74101.03.

19. Kint JA. Fabry's Disease: Alpha-Galactosidase Deficiency. *Science (80-)*. 1970;167(3922).

20. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an under-recognized multisystemic disorder: Expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Intern Med*. 2003;138:338-346. doi:10.7326/0003-4819-138-4-200302180-00014.

21. Brady RO, Schiffmann R. Clinical Features of and Recent Advances in Therapy for Fabry Disease. *JAMA*. 2000;284:2771-2775.

22. Pan X, Ouyang Y, Wang Z, et al. Genotype: A Crucial but Not Unique Factor Affecting the Clinical Phenotypes in Fabry Disease. Jefferies JL, ed. *PLoS One*. 2016;11(8). doi:10.1371/journal.pone.0161330.

23. Topaloglu AK, Ashley GA, Tong B, et al. Twenty novel mutations in the alpha-galactosidase A gene causing Fabry disease. *Mol Med*. 1999;5(12):806-811. http://www.ncbi.nlm.nih.gov/pubmed/10666480. Accessed February 6, 2017.

24. Deegan PB, Baehner AF, Romero M-B, et al. Natural history of Fabry disease in females in the Fabry Outcome Survey. *J Med Genet*. 2006;43:347-352. doi:10.1136/jmg.2005.036327.

25. Desnick RJ, Wasserstein MP, Banikazemi M. Fabry disease (alpha-galactosidase A deficiency): renal involvement and enzyme replacement therapy. *Contrib Nephrol*. 2001;136(136):174-192. http://www.ncbi.nlm.nih.gov/pubmed/11688379. Accessed January 26, 2017.

26. Ramaswami U, Whybra C, Parini R, et al. Clinical manifestations of Fabry disease in children: Data from the Fabry Outcome Survey. *Acta Paediatr Int J Paediatr*. 2006;95:86-92. doi:10.1080/08035250500275022.

27. Hopkin RJ, Bissler J, Banikazemi M, et al. Characterization of Fabry Disease in 352 Pediatric Patients in the Fabry Registry. *Pediatr Res*. 2008;64(5):550-555. doi:10.1203/PDR.0b013e318183f132.

28. Kolodny EH, Pastores GM. Anderson-Fabry Disease: Extrarenal, Neurologic Manifestations. *J Am Soc Nephrol*. 2002;13:S150-S153. doi:10.1097/01.ASN.0000015239.57436.18.

29. Stryker, Virginia L.; Kreps C. Fabry Disease: Though the condition may be rare, the suffering it imparts is severe. *Am J Nurs*. 2001;101(4):39-44. http://journals.lww.com/ajnonline/Citation/2001/04000/Fabry_Disease__Though_the_condition_may_be_rare,.19.aspx. Accessed January 26, 2017.

30. Albano LMJ, Rivitti C, Bertola DR, et al. Angiokeratoma: a cutaneous marker of Fabry's disease. *Clin Exp Dermatol*. 2009;35:505-508. doi:10.1111/j.1365-2230.2009.03721.x.

31. Laney DA, Gruskin DJ, Fernhoff PM, et al. Social-Adaptive and psychological functioning of patients affected by Fabry disease. *J Inherit Metab Dis*. 2010;33(Suppl 3):S73-S81. doi:10.1007/s10545-009-9025-6.

32. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P. Life expectancy and cause of death in males and females with Fabry disease: Findings from the Fabry Registry. *Genet Med*. 2009;11(11):790-796. doi:10.1097/GIM.0b013e3181bb05bb.

33. Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: Recommendations of the national society of genetic counselors. *J Genet Couns*. 2013;22:555-564. doi:10.1007/s10897-013-9613-3.

34. Gupta, Surya; Ries, Markus; Kotsopoulos, Steven; Schiffman R. The Relationship of Vascular Glycolipid Storage to Clinical Manifestations of Fabry Disease. *Medicine (Baltimore)*. 2005;84(5):261-268.

35. Kampmann C, Wiethoff CM, Perrot A, Beck M, Dietz R, Osterziel KJ. The heart in Anderson Fabry disease. *Z Kardiol*. 2002;91(10):786-795. doi:10.1007/s00392-002-0848-5.

36. Whybra C, Kampmann C, Willers I, et al. Anderson-Fabry disease: clinical manifestations of disease in female heterozygotes. *J Inherit Metab Dis*. 2001;24(7):715-724. http://www.ncbi.nlm.nih.gov/pubmed/11804208. Accessed February 6, 2017.

37. Maier E, Osterrieder S, Whybra C, et al. Disease manifestations and X inactivation in heterozygous females with Fabry disease. *Acta Paediatr Int J Paediatr*. 2006;95(0):30-38. doi:10.1080/08035320600618809.

38. Dobyns WB, Filauro A, Tomson BN, et al. Inheritance of most X-linked traits is not dominant or recessive, just X-linked. *Am J Med Genet*. 2004;129A(2):136-143. doi:10.1002/ajmg.a.30123.

39. Street NJ, Yi MS, Bailey LA, Hopkin RJ. Comparison of health-related quality of life between heterozygous women with Fabry disease, a healthy control population, and patients with other chronic disease. *Genet Med*. 2006;8(6):346-353. doi:10.1097/01.gim.0000223545.63012.5a.

40. Rozenfeld PA. Fabry disease: Treatment and diagnosis. *IUBMB Life*. 2009;61(11):1043-1050. doi:10.1002/iub.257.

41. Laney DA, Fernhoff PM. Diagnosis of Fabry disease via analysis of family history. *J Genet Couns*. 2008;17:79-83. doi:10.1007/s10897-007-9128-x.

42. Yasuda M, Shabbeer J, Benson SD, Maire I, Burnett RM, Desnick RJ. Fabry disease: Characterization of alpha-galactosidase A double mutations and the D313Y plasma enzyme pseudodeficiency allele. *Hum Mutat*. 2003;22(6):486-492. doi:10.1002/humu.10275.

43. Ashton-Prolla P. Fabry Disease: Twenty-Two Novel Mutations in the Alpha-Galactosidase a Gene and Genotype/Phenotype Correlations in Severely and Mildly Affected Hemizygotes and Heterozygotes - Journals - NCBI. *J Investig Med*. 2000;48(4):227-235. https://www.ncbi.nlm.nih.gov/labs/articles/10916280/. Accessed January 26, 2017.

44. Eng, Christine M., Guffon, Nathalie., Wilcox R. William. GPD. RECOMBINANT HUMAN a - GALACTOSIDASE A REPLACEMENT THERAPY IN FABRY'S DISEASE SAFETY AND EFFICACY OF RECOMBINANT HUMAN a - GALACTOSIDASE A. *English J*. 2001;345(1):9-16.

45. Eng CM, Banikazemi M, Gordon RE, et al. A Phase 1/2 Clinical Trial of Enzyme Replacement in Fabry Disease: Pharmacokinetic, Substrate Clearance, and Safety Studies. *Am J Hum Genet*. 2001;68:711-722.

46. Schiffmann R, Kopp JB, Austin III HA, et al. Enzyme Replacement Therapy in Fabry Disease. *JAMA*. 2001;285(21):2743-2749. doi:10.1001/jama.285.21.2743.

47. Hoffmann B, Garcia De Lorenzo A, Mehta A, Beck M, Widmer U, Ricci R. Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). *J Med Genet*. 2005;42:247-252. doi:10.1136/jmg.2004.025791.

48. Ramaswami U, Wendt S, Pintos-Morell G, et al. Enzyme replacement therapy with agalsidase alfa in children with Fabry disease. *Acta Paediatr Int J Paediatr*. 2007;96:122-127. doi:10.1111/j.1651-2227.2007.00029.x.

49. Spada M, Kasper D, Pagliardini V, Biamino E, Giachero S, Porta F. Metabolic progression to clinical phenotype in classic Fabry disease. *Ital J Pediatr*. 2017;43(1). doi:10.1186/s13052-016-0320-1.

50. Beck M, Hughes D, Kampmann C, et al. Long-term effectiveness of agalsidase alfa enzyme replacement in Fabry disease: A Fabry Outcome Survey analysis. *Mol Genet Metab Reports*. 2015;3:21-27. doi:10.1016/j.ymgmr.2015.02.002.

51. Kim JH, Lee BH, Hyang Cho J, et al. Long-term enzyme replacement therapy for Fabry disease: efficacy and unmet needs in cardiac and renal outcomes. *J Hum Genet*. 2016;61(11):923-929. doi:10.1038/jhg.2016.78.

52. Crosbie TW, Packman W, Packman S. Psychological aspects of patients with Fabry disease. *J Inherit Metab Dis*. 2009;32:745-753. doi:10.1007/s10545-009-1254-1.

53. Cole AL, Lee PJ, Hughes DA, Deegan PB, Waldek S, Lachmann RH. Depression in adults with Fabry disease: A common and under-diagnosed problem. *J Inherit Metab Dis*. 2007;30(6):943-951. doi:10.1007/s10545-007-0708-6.

54. Abreo K, Oberley TD, Gilbert EF, Opitz JM, Updike SJ. Clinicopathological conference: A 29-yr-old man with recurrent episodes of fever, abdominal pain, and vomiting. *Am J Med Genet*. 1984;18(2):249-264. doi:10.1002/ajmg.1320180209.

55. Lehmann A, Speight BS, Kerzin-Storrar L. Extended family impact of genetic testing: The experiences of x-linked carrier grandmothers. *J Genet Couns*. 2011;20:365-373. doi:10.1007/s10897-011-9360-2.

56. Gijsbers van Wijk CMT, van Vliet KP, Kolk AM, Everaerd WTAM. Symptom Sensitivity and Sex Differences in Physical Morbidity: A Review of Health Surveys in the United States and the Netherlands. *Women Health*. 1991;17(1):91-124. doi:10.1300/J013v17n01_06.

57. Malterud K, Horton R, Sassower R, et al. The art and science of clinical knowledge: evidence beyond measures and numbers. *Lancet*. 2001;358(9279):397-400. doi:10.1016/S0140-6736(01)05548-9.

58. Geroe K. Assessing Health Beliefs of Women Diagnosed and At-Risk for Fabry Disease. 2014. http://d-scholarship.pitt.edu/21041/.

59. Biegstraaten M, Arngrímsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet J Rare Dis*. 2015;10:36. doi:10.1186/s13023-015-0253-6.

60. Weidemann F, Niemann M, Sommer C, Beer M, Breunig F, Wanner C. Interdisciplinary approach towards female patients with Fabry disease. *Eur J Clin Invest*. 2012;42(4):455-462. doi:10.1111/j.1365-2362.2011.02614.x.

61. Connock M, Frew E, Mans A, Dretzke J. Enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1. *Health Technol Assess (Rockv)*. 2006;10(20).

62. Fu Y-H, Kuhl DPA, Pizzuti A, et al. Variation of the CGG repeat at the fragile X site results in genetic instability: Resolution of the Sherman paradox. *Cell*. 1991;67(6):1047-1058. doi:10.1016/0092-8674(91)90283-5.

63. Sherman S, Pletcher BA, Driscoll DA. Fragile X syndrome: diagnostic and carrier testing. *Genet Med*. 2005;7(8):584-587. doi:10.109701.GIM.0000182468.22666.dd.

64. Freund LS, Reiss AL, Abrams MT. Psychiatric Disorders Associated With Fragile X in the Young Female. *Pediatrics*. 1993;91(2). http://pediatrics.aappublications.org/content/91/2/321.long. Accessed March 10, 2017.

65. Jacquemont S, Hagerman RJ, Leehey MA, et al. Penetrance of the Fragile X–Associated Tremor/Ataxia Syndrome in a Premutation Carrier Population. *JAMA*. 2004;291(4):460. doi:10.1001/jama.291.4.460.

66. Allingham-Hawkins DJ, Babul-Hirji R, Chitayat D, et al. Fragile X premutation is a significant risk factor for premature ovarian failure: the International Collaborative POF in Fragile X study--preliminary data. *Am J Med Genet*. 1999;83(4):322-325. http://www.ncbi.nlm.nih.gov/pubmed/10208170. Accessed March 10, 2017.

67. Deeks AA, Gibson-Helm M, Teede H, Vincent A. Premature menopause: a comprehensive understanding of psychosocial aspects. *Climacteric*. 2011;14(5):565-572. doi:10.3109/13697137.2011.566390.

68. Gane LW, Iosif A-M, Flynn-Wilson L, Venturino M, Hagerman RJ, Seritan AL. Assessment of patient and caregiver needs in fragile X-associated tremor/ataxia syndrome by utilizing Q-sort methodology. *Aging Ment Health*. 2010;14(8):1000-1007. doi:10.1080/13607863.2010.501066.

69. Batshaw ML, Msall M, Beaudet AL, et al. Risk of serious illness in heterozygotes for ornithine transcarbamylase deficiency. *J Pediatr*. 1986;108(2):236-241. doi:10.1016/S0022-3476(86)80989-1.

70. McCullough BA, Yudkoff M, Batshaw ML, Wilson JM, Raper SE, Tuchman M. Genotype spectrum of ornithine transcarbamylase deficiency: Correlation with the clinical and biochemical phenotype. *Am J Med Genet*. 2000;93(4):313-319. doi:10.1002/1096-8628(20000814)93:4<313::AID-AJMG11>3.0.CO;2-M.

71. Msall M, Batshaw ML, Suss R, Brusilow SW, Mellits ED. Neurologic Outcome in Children with Inborn Errors of Urea Synthesis. *N Engl J Med*. 1984;310(23):1500-1505. doi:10.1056/NEJM198406073102304.

72. Ben-Ari Z, Dalal A, Morry A, et al. Adult-onset ornithine transcarbamylase (OTC) deficiency unmasked by the Atkins' diet. *J Hepatol*. 2010;52(2):292-295. doi:10.1016/j.jhep.2009.11.014.

73. Panlaqui OM, Tran K, Johns A, McGill J, White H. Acute hyperammonemic encephalopathy in adult onset ornithine transcarbamylase deficiency. *Intensive Care Med*. 2008;34(10):1922-1924. doi:10.1007/s00134-008-1217-2.

74. Chiong MA, Bennetts BH, Strasser SI, Wilcken B. Fatal late-onset ornithine transcarbamylase deficiency after coronary artery bypass surgery. *Med J Aust*. 2007;186(8):418-419. http://www.ncbi.nlm.nih.gov/pubmed/17437397. Accessed March 26, 2017.

75. Plug I, Mauser-Bunschoten EP, Brö Cker-Vriends AHJT, et al. Bleeding in carriers of hemophilia. *Blood*. 2006;108:52-56. doi:10.1182/blood-2005.

76. Paroskie A, Gailani D, DeBaun MR, Sidonio RF, Jr. A cross-sectional study of bleeding phenotype in haemophilia A carriers. *Br J Haematol*. 2015;170(2):223-228. doi:10.1111/bjh.13423.

77. Barlow JH, Stapley J, Ellard DR, et al. Living with haemophilia and von Willebrand's: a descriptive qualitative study. *Patient Educ Couns*. 2007;68(3):235-242. doi:10.1016/j.pec.2007.06.006.

78. Plug I, Peters M, Mauser-Bunschoten EP, et al. Social participation of patients with hemophilia in the Netherlands. *Blood*. 2008;111:1811-1815. doi:10.1182/blood-2007-07-102202.

79. Siboni SM, Mannucci PM, Gringeri a, et al. Health status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy. *J Thromb Haemost*. 2009;7(5):780-786. doi:10.1111/j.1538-7836.2009.03318.x.

80. Buxbaum NP, Ponce M, Saidi P, Michaels LA. Psychosocial correlates of physical activity in adolescents with haemophilia. *Haemophilia*. 2010;16(4):656-661. doi:10.1111/j.1365-2516.2010.02217.x.

81. Bottos AM, Zanon E, Sartori MT, Girolami A. Psychological aspects and coping styles of parents with Haemophilic child undergoing a programme of counselling and psychological support. *Haemophilia*. 2007;13(3):305-310. doi:10.1111/j.1365-2516.2006.01428.x.

82. Ghanizadeh A, Baligh-Jahromi P. Depression, anxiety and suicidal behaviour in children and adolescents with Haemophilia. *Haemophilia*. 2009;15(2):528-532. doi:10.1111/j.1365-2516.2008.01971.x.

83. Barlow JH, Stapley J, Ellard DR, Gilchrist M. Information and self-management needs of people living with bleeding disorders: a survey. *Haemophilia*. 2007;13(3):264-270. doi:10.1111/j.1365-2516.2007.01444.x.

84. Järvinen O, Lehesjoki AE, Lindlöf M, Uutela A, Kääriäinen H. Carrier testing of children for two X-linked diseases: A retrospective study of comprehension of the test results and social and psychological significance of the testing. *Pediatrics*. 2000;106(6):1460-1465. doi:10.1542/PEDS.106.6.1460.

85. Hunter LR, Lynch BA. Impact of Implementing Mental Health Screening by Mail With a Primary Care Management Model. *J Prim Care Community Health*. 2014;5(1):9-13. doi:10.1177/2150131913484340.

86. Fothergill KE, Gadomski A, Solomon BS, et al. Assessing the Impact of a Web-Based Comprehensive Somatic and Mental Health Screening Tool in Pediatric Primary Care. *Acad Pediatr*. 2013;13(4):340-347. doi:10.1016/j.acap.2013.04.005.

87. Rose GL, Ferraro TA, Skelly JM, et al. Feasibility of automated pre-screening for lifestyle and behavioral health risk factors in primary care. *BMC Fam Pract*. 2015;16(1):150. doi:10.1186/s12875-015-0368-9.